

**Wheelous, Teresa A**

---

**From:** Nighswander, Robbin M  
**Sent:** Tuesday, September 27, 2005 5:56 PM  
**To:** Peat, Raquel  
**Cc:** Colangelo, Kim M; Locicero, Colleen L; Wheelous, Teresa A  
**Subject:** RE: 505(b)(2): NDA 21-479, SELEGILINE HCL with a goal date of September 30, 2005



FW: 505b2  
Question for Zydis S.

Raquel:

I've attached Teresa's recent email on this.. does this help? Also, Teresa is back to work now so she is handling this application again.

Robbin

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

**From:** Peat, Raquel  
**Sent:** Tuesday, September 27, 2005 5:48 PM  
**To:** Nighswander, Robbin M  
**Cc:** Colangelo, Kim M; Locicero, Colleen L; Wheelous, Teresa A  
**Subject:** RE: 505(b)(2): NDA 21-479, SELEGILINE HCL with a goal date of September 30, 2005

Hi Robbin:

I am following up on this application. You indicated that the applicant has provided paragraph III certification to patent #5,648,093, which expires July 15, 2014. This patent is listed for risperidone (NDA 21-444). Was this patent certification provided in error, or if it was provided for the drug delivery technology (or something else related to the proposed product)?

Thanks and kind regards,

Raquel

LT Raquel Peat, MS, MPH, USPHS  
Regulatory Project Officer  
FDA/CDER/OND, Immediate Office  
301-796-0700 (OND IO main)  
301-796-0517 (direct)  
Fax: 301-796-9858

Address:  
10903 New Hampshire Ave.  
Bldg #22, Room 6469  
Silver Spring, MD 20993

**Appears This Way  
On Original**

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

Trade Name: Zelapar™  
Established Name: selegiline hydrochloride  
Dosage Form: Zydis® orally disintegrating tablets  
Strengths: 1.25 mg

Applicant: Valeant Pharmaceuticals International  
Agent for Applicant: William L. Schary

Date of Application: Original 3/29/02, Resubmission to Approvable Letter: 3/29/05  
Date of Receipt: Original 4/8/02, Resubmission: 3/30/05  
Date of Filing Meeting: Original 5/15/02  
Filing Date: 5/29/02

User Fee Goal Date: Resubmission: 9/30/05

Indication(s) requested: Adjunct to levodopa / carbidopa in management of patients with Parkinson's disease who exhibit deterioration in the quality of their response to this therapy.

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

NDA 19-334 Eldepryl Tablets &  
NDA 20-647 Eldepryl Capsules

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

Version: 12/15/04  
(OR) (HFD-007)?

YES  NO

(c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES  NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES  NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES  NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a change in dosage form; specifically, a rapidly-disintegrating tablet. The reference listed drug "Eldepryl" is approved as both immediate-release tablets and capsules.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES  NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES  NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
  - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
  - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

The sponsor, in a submission dated August 23, 2005, states the following:

**“Certifications for the listed drug.**

As provided in Section 1.2 and 1.3 (Item 1, Volume 1, Page15-16) of the original Zelapar™ NDA, filed in March 2002, the patent certification for the drug was addressed by providing the patent expiration date (e.g., 15 July 2014)(Attachment 2). Although not explicitly stated as such, this statement is essentially a “Paragraph III Certification,” as stipulated in §314.50(i)(1)(i)(a)(3).”

Patent number(s): 5,648,093 exp: July 15, 2014 Drug Product (Composition)

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the

Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES  NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A  YES  NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A  YES  NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES  NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES  NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 47,005 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES  NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES  NO

Robbin Nighswander  
Supervisory Regulatory Health Project Manager

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/

-----  
Robbin Nighswander  
9/7/2005 06:21:18 PM  
CSO

Appears This Way  
On Original

# MEMORANDUM

**To:** Teresa Wheelous  
Division of Neurology Drugs, HFD-120

**From:** Iris Masucci  
DDMAC, HFD-042

**Date:** September 1, 2005

**Re:** Comments on draft labeling for Zelapar (selegiline) orally  
disintegrating tablets  
NDA 21-479

---

I have reviewed the proposed label for Zelapar and offer the following comments:

## Clinical Studies

7  
[-----]

b(4)

b(5)

Does this information on long-term Zelapar use represent substantial evidence? If not, we recommend its deletion from the label.

7

b(4)

7

b(5)

This paragraph presents results for endpoints other than the previously identified primary endpoint (reduction in average percentage daily OFF time from baseline to the end of the trial). If these are secondary or exploratory endpoints that are not adequately supported, we recommend their deletion from the label.

## Figure 1

This graphic presents p-values at all time points during the trial. Did the study design and data analysis plan allow for statistical interpretation at multiple endpoints? The stated primary endpoint used an average of the 10- and 12-week data. In addition, the scale for the x-axis incorrectly presents the same width for the one-week intervals between

baseline, 1 week and 2 weeks as it does for the remaining 2-week intervals. If this table remains in the label, please re-scale the x-axis correctly.

b(4)

b(5)

As above, if these data are not considered substantial evidence, we recommend their deletion. Moreover, the results seem to be presented selectively, including only those that achieved statistical significance.

### Indications and Usage

We note that the indication section in the Eldepryl label includes the following sentence: "There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy." Should the same sentence be added to the Zelapar indication for consistency?

### Contraindications

"ZELAPAR™ is contraindicated for use with meperidine

b(4)

While we note that this sentence appears in the Eldepryl label, the wording is strange. What are we really trying to say with "

b(5)

### Warnings

b(4)

b(5)

Should the first sentence say "MAO-A" or MAO-B"? Also, is the recommendation about 10 mg a day based on any actual data or is it speculative? If the latter is true, is it truly helpful to the clinician?

"Obviously, any selectivity is further diminished with increasing daily doses."

b(4)

b(5)

Why does this statement single out \_\_\_\_\_ Should the same be true for any selegiline product, including Zelapar?

b(4)

b(5)

**Precautions – Irritation of the Buccal Mucosa**

[

]

b(4)

b(5)

We recommend deletion of this sentence from this precaution because it minimizes the risk of buccal mucosa irritation from Zelapar use.

**Adverse Events – Incidence in Controlled Clinical Trials**

The main adverse events table presents the event rates in alphabetical order within each body system. The draft guidance on the Adverse Events section of labeling recommends that events be listed in order of decreasing frequency within each body system, not alphabetically.

**Adverse Events – Other Adverse Events Observed During all Clinical Trials**

We recommend deletion of this entire section from the label. The draft guidance on the Adverse Events section in labeling recommends that “long and exhaustive lists of adverse events, including those that are infrequent, commonly observed in the absence of drug therapy, or not plausibly related to drug therapy, should be avoided.”

**Overdosage – Treatment Suggestions for Overdose**

[

]

b(4)

b(5)

The current recommendation in the poison control community is to encourage the use of the national toll-free number for centers rather than referring to the often outdated *PDR*. We suggest something like, “\_\_\_\_\_”

[

]

b(4)

b(5)

**Dosage and Administration**

[

]

b(4)

b(5)

We recommend rewording of this sentence to delete the discussion of ~~\_\_\_\_\_~~  
Such language generally does not appear in the Dosage and Administration section.

b(4)

b(5)

---

We recommend this sentence be merged with the last paragraph in this section that discusses how the product should be taken. If it remains standing alone, the reader may not the recommendations at the end of the section about not eating or drinking 5 minutes before and after taking it.

b(4)

b(5)

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/

-----  
Michael Brony  
9/1/2005 02:56:02 PM  
DDMAC REVIEWER

Appears This Way  
On Original



NDA 21-479

VALEANT Pharmaceuticals International  
Attention: William L. Schary, PhD  
Vice President, Regulatory Affairs  
3300 Hyland Avenue  
Costa Mesa, CA 92626

Dear Dr. Schary:

Please refer to your March 29, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zydis (selegiline hydrochloride) tablets.

The Division of Neuropharmacological Drug Products is currently investigating a possible **association of anti-Parkinson's disease therapies and malignant melanoma**. In order to estimate a background rate of melanoma in the population of **Parkinson's disease patients, the Division** plans to construct a database to track melanoma cases and person-time exposure in placebo-controlled, active treatment-controlled, and combined placebo- and active-controlled short term **studies of Parkinson's disease therapies**, as well as longer term open extension studies.

We request your participation in this effort by submitting the datasets described below, submitted as SAS transport files (x-port engine). The data request, detailed in the attachment, asks that you review the data from the trials of your drug **product in Parkinson's disease** and submit the number of melanoma cases and the person-time exposure data from both the randomized controlled trials and the open label trials. We have attached sample datasets to provide an example of how the data should be structured. Please also provide a list of trials by number and title of the trial. If it is not clear from the title of the study, please indicate whether the active drug was used as an adjunct to levodopa or as monotherapy. Do not include data from crossover trials. Please include a glossary with any abbreviations used.

Please also submit a narrative summary describing each case of melanoma identified during your development program. Be as specific as possible regarding the stage of the melanoma at diagnosis and whether the lesion was present prior to the initiation of the trial (e.g., at screening). If there is a pathology report available, include it. If at all possible, the tumor should be described as either invasive or local.

We appreciate your participation in this project so we can evaluate **the association of Parkinson's disease therapies with melanoma**.

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

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Attachment 1: Description of variables in requested datasets  
Attachment 2: Sample datasets

Appears This Way  
On Original

## ATTACHMENT 1

**CONTROLLED TRIAL FILE** - this file should contain trial design and overall enrollment information about each controlled trial, leading to one row per trial. Please provide the variables in the same order as shown below.

- **(TRIAL)** – trial identifier;
- **(LOC)** – geographic locations of study centers;  
[CODE: 1=North American centers only (e.g., US/Canada); 2=Non-North American centers only; 3=both North American and Non-North American Centers]
- **(TYEAR)** – calendar year trial was initiated;
- **(CTRL)** – describes type of trial control used;  
[CODE: P= placebo-controlled; A=active-controlled; PA= placebo- and active-controlled]
- **(DUR)** – duration of trial in weeks
- **(SET)** – setting trial population drawn from;  
[CODE: I= inpatient; O=outpatient; IO=inpatient and outpatient]
- **(TXRI)** – name of run-in treatment (drug name or placebo); NA if trial design did not include a run-in phase;
- **(TXI)** – name of post-randomization investigational treatment (drug name);
- **(TXAC)** – name of post-randomization active control treatment (drug name); NA if trial design did not include an active control;
- **(LEVOADJ)** – investigational treatment is being studied as an adjunct to levodopa (i.e., all enrolled patients are taking levodopa concomitantly with study drug);  
[CODE: Y =yes, N=no, U= unknown]
- **(RI)** – number of patients entering run-in phase; NA if trial design did not include a run-in phase;
- **(RIE)** – number of patients who actually received at least one dose of run-in treatment; NA if design did not include a run-in phase;
- **(RANI)** – number of patients randomized to investigational treatment;
- **(RANPC)** – number of patients randomized to placebo control; NA if trial design did not include a placebo control;
- **(RANAC)** – number of patients randomized to active control; NA if trial design did not include active control;
- **(RANEI)** – number of patients who actually received at least one dose of post-randomization investigational treatment;
- **(RANEPC)** – number of patients who actually received at least one dose of post-randomization placebo control; NA if trial design did not include a placebo control;
- **(RANEAC)** – number of patients who actually received at least one dose of post-randomization active control; NA if trial design did not include an active control;
- **(MRI)** – number of melanomas diagnosed during run-in phase; NA if trial design did not include a run-in phase;
- **(MI)** – number of post-randomization melanomas diagnosed in patients on investigational treatment;
- **(MPC)** – number of post-randomization melanomas diagnosed in patients on placebo control; NA if trial design did not include a placebo control;
- **(MAC)** – number of post-randomization melanomas diagnosed in patients on active control; NA if trial design did not include an active control;

**BEST POSSIBLE COPY**

**EXTENSION TRIAL FILE** - this file should contain trial design and overall enrollment information about each extension trial, leading to one row per trial. Please provide the variables in the same order as shown below.

- **(TRIAL)** – trial identifier;
- **(LOC)** – geographic locations of study centers;  
[CODE: 1=North American centers only (e.g., US/Canada); 2=Non-North American centers only; 3=both North American and Non-North American Centers]
- **(TYEAR)** – calendar year trial was initiated;
- **(CTRL)** – describes type of trial control used;  
[CODE: A= active-controlled; O= open]
- **(DUR)** – duration of trial in weeks
- **(SET)** – setting trial population drawn from;  
[CODE: I= inpatient; O= outpatient; IO= inpatient and outpatient]
- **(TXI)** – name of extension investigational treatment (drug name);
- **(TXAC)** – name of extension active control (drug name); NA if trial design did not include an active control;
- **(EXTI)** – number of patients enrolled in investigational treatment;
- **(EXTAC)** – number of patients enrolled in active control; NA if trial design did not include active control;
- **(EXTEI)** – number of patients who actually received at least one dose of extension investigational treatment;
- **(EXTEAC)** – number of patients who actually received at least one dose of extension active control; NA if trial design did not include an active control;
- **(MI)** – number of melanomas diagnosed in patients on investigational treatment;
- **(MAC)** – number of melanomas diagnosed on active control; NA if trial design did not include an active control;

**Controlled trials -PATIENT FILE:** this file should contain the following variables for each patient participating in a controlled trial, leading to one row per patient. Please provide the variables in the same order as shown below.

- **(TRIAL)** – trial identifier;
- **(CTPID)** – controlled trial patient identifier;
- **(AGE)** – patient age in years [U= unknown];
- **(GEN)** – patient gender [CODE: M= male; F=female; U= unknown];
- **(RACE)**- patient race [CODE: W= White; B= Black; A= Asian; O= Other];
- **(LEVOYRS)**- duration of prior levodopa therapy in years; enter 0 if none;
- **(LEVO)** – patient was taking levodopa concomitantly with the study drug  
[CODE: Y= yes; N=no, U= unknown];
- **(RITX)** – run-in treatment for this patient (drug name or placebo); NA if trial design did not include a run-in phase;
- **(FDRI)** – date of first dose of run-in treatment; NA if trial design did not include a run-in phase;
- **(LDRI)** – date of last dose of run-in treatment; NA if trial design did not include a run-in phase;
- **(RANTX)** – randomized treatment for this patient (name of investigational treatment, placebo, or name of active control treatment; NA if patient discontinued or died during run-in);

**BEST POSSIBLE COPY**

- **(FDRAN)** – date of first dose of randomized treatment;
- **(LDRAN)** – date of last dose of randomized treatment;
- **(RESCUE)** – patient started levodopa during study as a “rescue” medication  
[CODE: Y= yes; N= no, U= unknown];
- **(FDRESC)** -date of first dose of rescue treatment; NA if patient did not require rescue medication;
- **(RIDX)** – patient diagnosed with melanoma during run-in phase  
[CODE: Y= yes; N= no];
- **(RANDX)** – patient diagnosed with melanoma after randomization  
[CODE: Y= yes; N=no; RI=patient diagnosed during run-in];
- **(DDATE)** – date of diagnosis of melanoma  
[Enter the date; U= unknown; NA= patient did not have melanoma];
- **(DD30)** – melanoma diagnosed within 30 days of last dose of study treatment  
[CODE: Y= yes; N=no; U=unknown; NA= patient did not have melanoma]

**Extension trials- PATIENT FILE:** this file should contain the following variables for each patient participating in an extension trial, leading to one row per patient. Please provide the variables in the same order as shown below.

- **(TRIAL)** – trial identifier;
- **(CTPID)** – controlled trial patient identifier;
- **(EXTPID)** – extension trial patient identifier (if different from CTPID);
- **(AGE)** – patient age in years [U= unknown];
- **(GEN)** – patient gender [CODE: M= male; F= female; U= unknown];
- **(RACE)**- patient race [CODE: W= White; B= Black; A= Asian; O= Other];
- **(RANTX)** – randomized treatment for this patient (name of investigational treatment, placebo, or name of active control treatment);
- **(EXTTX)** – extension treatment for this patient
- **(LEVO)** – patient was taking levodopa concomitantly with the extension treatment  
[CODE: Y= yes; N= no, U= unknown];
- **(FDEX)** – date of first dose of extension treatment;
- **(LDEX)** – date of last dose of extension treatment;
- **(RESCUE)** – patient started levodopa during study as a “rescue” medication  
[CODE: Y =yes; N= no, U= unknown];
- **(FDRESC)** -date of first dose of rescue treatment; NA if patient did not require rescue medication;
- **(EXTDX)** – patient was diagnosed with melanoma during extension  
[CODE: Y =yes; N= no; RCT= patient diagnosed during controlled trial];
- **(DDATE)** – date of diagnosis of melanoma  
[Enter the date; U= unknown; NA= patient did not have melanoma];
- **(DD30)** – melanoma diagnosed within 30 days of last dose of study treatment  
[CODE: Y =yes; N= no; U= unknown; NA= patient did not have melanoma]

**BEST POSSIBLE COPY**

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/

-----  
Russell Katz

8/9/05 04:45:37 PM

Appears This Way  
On Original

**REQUEST FOR CONSULTATION**

TO (Division/Office):

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
PKLN Rm. 6-34**

FROM:

**Division of Neurology Products (DNDP), HFD-120, WOC2  
4<sup>th</sup> floor**

DATE

August 2, 2005

IND NO.

NDA NO.

21-479

TYPE OF DOCUMENT

Draft Labeling

DATE OF DOCUMENT

March 29, 2005

NAME OF DRUG

Zelapar

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

Standard

DESIRED COMPLETION DATE

September 15, 2005

NAME OF FIRM: **Elan Pharmaceuticals, Inc.**

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                       |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                              |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                   |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                         |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                  |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:**

Attached please find a copy of the sponsor's proposed labeling for this NDA for your review and comment. This labeling is being submitted in response to an Agency Approvable letter.

The user fee date for this application is 9/30/05

Thank you,  
Teresa Wheeler 301-594-5504

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

-----  
Teresa Wheelous  
8/2/05 05:20:19 PM

Appears This Way  
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office): <b>Mail: ODS / DDMAC (Room 15B-08, PKLN Bldg.)</b>			FROM: <b>Division of Neurology, HFD-120, WOC II - 4<sup>th</sup> floor</b>		
DATE <b>August 2, 2005</b>	IND NO.	NDA NO. <b>21-479</b>	TYPE OF DOCUMENT Labeling Response to Approvable Letter	DATE OF DOCUMENT <b>March 29, 2005</b>	
NAME OF DRUG <b>Zelapar (selegiline hydrochloride orally disintegrating) tablets</b>		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG <b>505(b)2</b>	DESIRED COMPLETION DATE <b>September 3, 2005</b>	
NAME OF FIRM: VALEANT Pharmaceutical Industries, LTD					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>					
<p>Please review the labeling for this NDA. This labeling is submitted in response to an approvable letter issued on February 7, 2003. The labeling response, dated March 29, 2005, to the approvable letter, can be found in the EDR \\Cdsub1\N21479\N_000\2005-03-31\labeling</p> <p>We plan to act on this application on September 30, 2005, the action at this time is not decided.</p> <p>Thank you, Teresa Wheelous (301) 594-5504</p>					
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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/

-----  
Teresa Wheelous  
8/2/05 04:57:33 PM

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-479

VALEANT Pharmaceuticals International  
Attention: William L. Schary, PhD  
Vice President, Regulatory Affairs  
3300 Hyland Avenue  
Costa Mesa, CA 92626

Dear Dr. Schary:

Please refer to your March 29, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for selegiline hydrochloride orally disintegrating tablets.

We acknowledge receipt on March 30, 2005, of your March 29, 2005 resubmission to your new drug application for selegiline hydrochloride orally disintegrating tablets.

We consider this a complete, class 2 response to our February 7, 2003 action letter. Therefore, the user fee goal date is **September 30, 2005**.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. However, we are waiving the requirement for pediatric studies for this application.

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

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

-----  
**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  
7/13/05 11:36:21 AM  
signed for Russell Katz, M.D.

Appears This Way  
On Original

**Wheelous, Teresa A**

---

**From:** Wheelous, Teresa A  
**Sent:** Friday, April 22, 2005 8:29 AM  
**To:** 'Anil Hiteshi'  
**Subject:** NDA 21-479 Zydis Selegiline Clin Pharm Info Request

Anil,

The Zydis selegiline Clin. Pharm. reviewer has the following information request:

Comment regarding Study RNA-ZEL-B-21-102 (Tyramine Challenge Study)

1. NARDIL tablets were overencapsulated for blinding purposes. The sponsor has not provided any in vitro dissolution data to show similarity between the NARDIL tablets and overencapsulated NARDIL tablets by F2 comparisons. The sponsor should provide this data for acceptability of the results obtained from Study RNA-ZEL-B-21-102.
2. The maximum study sample storage from the first blood draw to the last sample was 49 days. The sponsor has provided long term stability data for only 8 days so far. Please provide additional long term stability data to support the PK data.
3. Is trough PK data available from all subjects at Day 8 and 9. If yes, please indicate its location in the submission and also provide an assessment of the attainment of steady state in all subjects by evaluating trough data from Days 8, 9 and 10.

Thank you,  
Teresa

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-479

VALEANT Pharmaceuticals International  
Attention: William L. Schary, V.P. Regulatory Affairs  
3300 Hyland Avenue  
Costa Mesa, CA 92626

Dear Dr. Schary:

Please refer to your New Drug Application (NDA) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Zydis Selegiline (selegiline hydrochloride) Orally Disintegrating Tablet.

We also refer to your February 16, 2005, correspondence, received February 17, 2005, requesting a meeting to discuss the outstanding deficiencies referenced in an February 4, 2005 Agency letter.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: March 9, 2005  
Time: 3:45 PM – 4:30 PM  
Phone Arrangements: 301-594-6649

CDER Participants: To be determined

If you have any questions, call me at, at (301) 594-5504.

Sincerely,

*{See appended electronic signature page}*

CDR Teresa Wheelous  
Sr. Regulatory Project Manager  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

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

/s/

-----  
Teresa Wheelous  
3/4/05 04:40:19 PM

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-479

VALEANT Pharmaceuticals International  
Attention: William L. Schary, V.P. Regulatory Affairs  
3300 Hyland Avenue  
Costa Mesa, CA 92626

Dear Dr. Schary:

Please refer to your New Drug Application (NDA) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Zydis Selegiline (selegiline hydrochloride) Orally Disintegrating Tablet.

We also refer to your February 16, 2005, correspondence, received February 17, 2005, requesting a meeting to discuss the outstanding deficiencies referenced in an February 4, 2005 Agency letter.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: DATE

Time: TIME

Phone Arrangements: CALL-IN NUMBER AND PASSCODE ("Meet-me" Call)  
OR [REDACTED] will call [REDACTED] at PHONE NUMBER.

CDER Participants: PARTICIPANTS

Provide the background information for this meeting (three copies to the [REDACTED] and INSERT NUMBER desk copies to me) at least [REDACTED] prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by DATE, we may cancel or reschedule the meeting.

If you have any questions, call NAME, Regulatory Project Manager, at (301) NUMBER.

Sincerely,

{See appended electronic signature page}

NAME

NDA 21-479

Page 2

TITLE

Division of DIVISION NAME

Office of Drug Evaluation XX

Center for Drug Evaluation and Research

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/

-----  
Teresa Wheelous  
3/4/05 04:23:50 PM

Appears This Way  
On Original

Telecon Request Granted 022205.txt

To: Anil Hiteshi  
Subject: RE: Teleconference Request for NDA 21-479; March 9, 2005

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

From: Anil Hiteshi [mailto:ahiteshi@valeant.com]  
Sent: Wednesday, February 23, 2005 5:56 PM  
To: WHEELOUST@cder.fda.gov  
Cc: William Schary; Rory Turk  
Subject: Teleconference Request for NDA 21-479; March 9, 2005

Dear Teresa,

To follow-up with my voice mail message, I am sending a written response to inform you that we are available on March 9, 2005 at 3:45 PM (EST) for a teleconference with DNDP. This teleconference was requested by Valeant on February 16, 2005 to seek additional guidance from the Agency regarding the exact content of the requested safety update.

Please confirm that the 3:45 PM time slot for the teleconference is for eastern standard time (12:45 PM PST).

Thank you.

Kind regards,

Anil.

-----  
Anil K. Hiteshi, R.A.C.  
Associate Director, Regulatory Affairs  
Valeant Pharmaceuticals International  
3300 Hyland Avenue  
Costa Mesa, CA 92626  
Tel: (714) 545-0100, x3057  
Fax: (714) 641-7281  
ahiteshi@valeant.com

----- Forwarded by Anil Hiteshi/Research/ICN on 02/23/2005 02:25 PM -----

William Schary

To: Anil Hiteshi/HQ/ICN@ICN

02/23/2005 10:12

cc:

AM

Subject: Fw: Telecon Request for

NDA 21-479

Hello Anil,

Telecon Request Granted 022205.txt

Please confirm with Teresa.

Bill

-----  
Sent from William's BlackBerry Wireless Handheld

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

From: "Wheelous, Teresa A" [WHEELOUST@cder.fda.gov]

Sent: 02/23/2005 07:53 AM

To: William Schary

Subject: Telecon Request for NDA 21-479

Dr. Schary,

The Feb. 16, 2005 telecon request for NDA 21-479 zydis selegiline has been granted.

The next available afternoon time slot is March 9, 2005 at 3:45 PM.

Let me know if this date and time works for you.

Thank you,

CDR Teresa Wheelous, R. Ph.  
Senior Regulatory Management Officer  
Office of Drug Evaluation I  
Division of Neuropharmacological Drug Products  
HFD-120  
1451 Rockville Pike  
Rockville, MD 20852  
Telephone (301) 594-2850  
Fax (301) 594-2859

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

/s/

Teresa Wheelous  
3/4/05 04:31:35 PM

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-479

VALEANT Pharmaceuticals International  
Attention: William L. Schary, V.P. Regulatory Affairs  
3300 Hyland Avenue  
Costa Mesa, CA 92626

Dear Dr. Schary:

We acknowledge receipt on December 16, 2004 of your December 15, 2004 submission to your new drug application (NDA) for Zydys Selegiline (selegiline hydrochloride) Orally Disintegrating Tablet.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies still need to be addressed:

**CLINICAL**

1. There is no Table of Contents for the entire 18-volume submission. While a rudimentary Index indicating major items in the submission has been provided, the location of these items by volume and page number is not listed. This Index does not substitute for a Table of Contents which specifies the precise location of items. The overall Table of Contents should specify major items as well as significant "minor" items and their location by volume and page.

For the 2 study reports, you provided a Table of Contents of items/sections of the study reports and provided page locations for the items/sections and for in-text tables and figures. However, you did not specify the location of the many post-text tables and figures, or the numerous items in the Appendices for both of these large study reports. Without identifying specific locations of these various items by volume and page, the reviewer has to page through the many pages of various volumes instead of going to the specific location of the desired item. In addition, there are no page numbers on the pages after the narrative portion of the study report.

Please submit an overall Table of Contents for the entire submission identifying major and significant "minor" items together with the specific location by volume and page number, and designate a page number for each page of each volume.

Please submit a comprehensive Table of Contents for each of the 2 study reports. Each Table of Contents should specify the volume and page location of each item in the Table of Contents including each post-text table and figure, each data listing, and each specific item described in the Appendices.

2. You did not provide the analyses of adverse oropharyngeal reactions that should have been provided in this submission. The labeling provided in the Approvable letter requested information about oropharyngeal adverse reactions. Subsequent to the issuance of this letter, there were numerous communications (mostly via e-mail) between Elan (the sponsor at that time) and the DNDP. In these e-mails, Elan had requested guidance about how to address the request in the label, the DNDP provided guidance, and Elan provided responses about DNDP's guidance and recommendations.

You should obtain these e-mail communications from Elan, review them and contact us if you have any questions. Please contact us if you are not able to obtain these e-mail communications.

#### **NON- DEFICIENCY INFORMATION REQUESTS**

The following are not deficiencies, but are information requests that have been identified during our cursory review of your response:

##### **CLINICAL**

##### **Safety Information**

Although we did not request a safety update in our Approvable Letter we recognized that a Safety Update is necessary. Ordinarily, a Response to an Approvable Letter contains a Safety Update relative to the last Safety Update provided. The last Safety Update submitted (11/8/02) for Zydis selegiline for NDA 21479 had a cut-off date for safety data that was 12/31/01. There were 92 patients that continued receiving Zydis selegiline in this study after the cut-off date. Based upon the Study Report Z/SEL/97/027, this study was completed on 1/8/03. Thus, up to 92 patients were treated with Zydis selegiline for various periods up to over 1 year. A full Safety Update must be submitted. This Safety Update should show the safety experience of all patients treated with Zydis selegiline in all clinical trials (including any other clinical trials other than Study 027) after the last safety cut-off date (12/31/01). "New" data in the Safety Update should be presented in a format that compares this most recent safety experience with the experience shown in the last Safety Update.

Please also provide a summary of the safety experience of healthy subjects who participated in clinical pharmacology studies assessing pharmacokinetic and/or pharmacodynamic endpoints as was done in the original submission of NDA 21-479. This summary of the safety experience should include all subjects who participated in pharmacokinetic and/or pharmacodynamic studies and provide updated information since the last cut-off date in which such experience was summarized in the initial review cycle. This summary should also compare and contrast the updated safety information with the information collected in patients who participated in clinical studies of Zydis selegiline that was provided in the initial review cycle.

We have requested information from you about when the last patient was treated in a clinical study but have not yet received a response. This would have helped us evaluate the need for a safety update.

When you respond please include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

Present tabulations of the new safety data separately and these new data combined with the cumulative experience of the original NDA data and last Safety Update to compare with the cumulative experience shown in the last Safety Update. These tabulations should contain 3 columns of safety experience.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
  4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
  5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
  6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
  7. Provide English translations of current approved foreign labeling not previously submitted.

#### Labeling with Tracked Changes

Please submit a paper copy of the "tracked changes" version of your revised label using the label included with the Approvable letter as the base document and showing any of your edits/changes as cross-outs/deletions or additions/underlined. You provided a "clean" copy of your proposed

label and an annotated copy of your proposed label. However, your annotated copy does not show your additions to the label provided in the Approvable letter. We are not certain whether your strikeouts/deletions contained in this annotated version are complete. A tracked changes version of the label showing the Approvable label as the base document and showing all deletions as strike-outs and all additions as underlines is a critical document that helps us review your proposed revisions. Please submit an electronic copy of your "tracked changes" version of the label in WORD format.

Copies of Emails and Valeant Responses to DNDP Requests

Please incorporate any responses that you have provided in response to questions or requests (often via e-mail) for clarification from the DNDP into appropriate sections of the Response to the Approvable Letter. This request refers to various e-mail communications that you have had with DNDP over the past few months.

Tyramine Sensitivity Factor / Tyramine Pressor Ratio

Please provide information about the Tyramine Sensitivity Factor/Tyramine Pressor Ratio (TSF/TPR) for subjects who were studied in Study RNA-ZEL-B21-102. The TSF/TPR is defined as the dose of tyramine showing a threshold response at baseline/post-treatment. Provide data for 2 threshold definitions: 1) the dose of tyramine necessary to produce an increase in systolic blood pressure of  $\geq 30$  mm Hg relative to the mean pretreatment value; and 2) the dose of tyramine necessary to produce an increase in systolic blood pressure of  $\geq 30$  mm Hg relative to the mean pretreatment value on 2 consecutive measurements. Please provide :1) a listing of these results for all subjects according to treatment group; and 2) statistical analyses comparing mean data for each different tyramine threshold across all treatment groups.

Date that the Last Subject Exited

Please clarify the date on which the last subject exited from Study RNA-ZEL-B21-102. We would consider the date upon which the last subject exited the study as the study completion date. The report for Study RNA-ZEL-B21-102 notes that the study completion date was August 25, 2004, but your e-mail (1/11/05) specifies that "The last subject exited the study on September 23, 2004." Would you please clarify this apparent discrepancy?

Because our reviewers have not conducted a complete review of your response to the Approvable Letter, you should not conclude that the problems or deficiencies identified in this letter are the only ones that exist in this response. You should conduct a careful review of this response relative to the Approvable letter to determine if other problems or deficiencies that have not yet been identified or described in this letter might also exist. Other problems or deficiencies that you might identify but which are not outlined in this letter should be addressed and corrected as well as the ones that we have identified.

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS**

1. Please submit the individual QT Data from Study RNA600301-101 electronically as SAS transport (.xpt) files. The following format should be adopted for this dataset. If you have any questions regarding data organization please request a telecon with the Office of Clinical Pharmacology and Biopharmaceutics.

Variable	Description	Units
ID	Unique ID # for each patient (maximum of 6 numbers)	--
TIME	Time from the <b>first</b> observation	hours
DV	drug concentration or QT interval (round to nearest thousandth) When AMT <= 0, DV =.	ug/L msecs
TYPE	1=QT 2=drug concentration	--
AMT	Dose	mg
RR	Measured RR (round to nearest thousandth)	secs
HR	Measured HR	bpm
HT	Height (round to nearest tenth)	cm
WT	Weight (round to nearest tenth)	kg
AGE	Age	years
RACE	Race 1=white 2=black 3=Hispanic 4=Asian	--
SEXM	0=female 1=male	--
MTIME	Military time	hh:mm
DATE	date	mm-dd-yyyy

2. Please submit electronic data in SAS transport files for the Study RNA-ZEL-B21-102. This dataset should include individual blood pressure data for tyramine challenge at baseline and post treatment, change in blood pressure post treatment, orthostatic blood pressure data pre and post treatment, dose, drug concentration measurement etc.

#### PRECLINICAL

Please provide a timeline for the Phase 4 commitment:

A complete battery of reproductive and developmental toxicology and genotoxicity studies as a Phase 4 commitment (cf. *Guideline for Industry - Detection of Toxicity to Reproduction for Medicinal Products*; ICH-S5A, Sept 1994; *A Standard Battery for Genotoxicity Testing of Pharmaceuticals*; ICH-S2B, Jul 1997). The *in vivo* studies should be conducted using a route of administration that will result in plasma exposure to selegiline and major metabolites exceeding those expected in humans at the maximum recommended clinical dose.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and

NDA 21-479

Page 6

effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

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

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Division Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/

-----  
Russell Katz  
2/4/05 11:57:56 AM

Appears This Way  
On Original

**Wheelous, Teresa A**

---

**From:** Anil Hiteshi [ahiteshi@valeant.com]  
**Sent:** Thursday, January 27, 2005 5:53 PM  
**To:** WHEELOUST@cder.fda.gov  
**Cc:** William Schary  
**Subject:** RE: Requested Response on the Oropharyngeal Examination Data



cvr ltr.pdf (103 KB) form fda 356h.pdf (217 KB)



new analysis + appendix 1.pdf ...



table1.pdf (108 KB) table 11-a.pdf (85 KB)



table 6.1a.pdf (326 KB)



appendix 2.pdf (120 KB)



appendix 3.pdf (49 KB)

Dear Teresa,

In response to Dr. Kapcala request of January 10, 2005, attached please find a copy of the submission sent via overnight delivery to your attention today.

Thank you. If you or Dr. Kapcala have any further comments, please do not hesitate to contact us.

Kind regards,

Anil.

(See attached file: cvr ltr.pdf) (See attached file: form fda 356h.pdf) (See attached file: new analysis + appendix 1.pdf) (See attached file: table1.pdf) (See attached file: table 11-a.pdf) (See attached file: table 6.1a.pdf) (See attached file: appendix 2.pdf) (See attached file: appendix 3.pdf)

-----  
Anil K. Hiteshi, R.A.C.  
Associate Director, Regulatory Affairs  
Valeant Pharmaceuticals International  
3300 Hyland Avenue  
Costa Mesa, CA 92626  
Tel: (714) 545-0100, x3057  
Fax: (714) 641-7281  
ahiteshi@valeant.com

----- Forwarded by Anil Hiteshi/Research/ICN on 01/27/2005 02:26 PM -----

William Schary

01/25/2005 05:15 PM

To: Anil Hiteshi/HQ/ICN@ICN  
cc:  
Subject: RE: Requested Responses

Hello Anil,

Attached is the email from Kapcala requesting the OP data.

bill

----- Forwarded by William Schary/Research/ICN on 01/25/2005 05:14 PM -----

"Kapcala, Leonard  
P"  
<wlschary@icnpharm.com>  
<rturk@ribapharm.com>, "Kapcala, Leonard P"  
a.gov>  
01/10/2005 08:38  
AM

To: "'William Schary'"  
cc: "'rturk@ribapharm.com'"  
<KAPCALAL@cdcr.fda.gov>  
Subject: RE: Requested Responses

Hi Dr. Schary,

I am asking where are the analyses of oropharyngeal adverse reactions from both pivotal trials that were supposed to have been submitted? The draft label had requested information about oropharyngeal adverse reactions. We then had numerous e-mail communications between Elan and us giving guidance about how to conduct these analyses. There was also a draft table constructed by Elan. Would you please tell us where is the specific location (volume and page) of these analyses in your Response to the Approvable Letter?

I hope that you can get back to me about this today as it is very important for me to find these quickly, hopefully today.

I also look forward to hearing the other various information (including date tyramine trial completed with last subject study exit) that you said you should provide to me today.

Thanx.

Best regards,

Len 301-594-5521

Rory Turk [rturk@ribapharm.com]

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

From: William Schary [mailto:wlschary@icnpharm.com]  
Sent: Friday, January 07, 2005 2:51 AM  
To: Kapcala, Leonard P  
Cc: Anil Hiteshi; Rory Turk  
Subject: RE: Requested Responses

Good morning Dr. Kapcala,

I have requested the information from our contractors and should have the information when I return to the office on Monday. I will forward not later than Monday.

Regards,

Bill

"Kapcala, Leonard

P"  
wlschary@icnpharm.com>  
<KAPCALAL@cder.fda.gov>  
a.gov>

To: "'William Schary'"  
cc: "Kapcala, Leonard"  
Subject: RE: Requested

Responses

01/06/2005 08:32

AM

Hi Dr. Schary,

Thank you for your response. I have a few questions about dates. When did Valeant decide to resume the study? When was the study completed in terms of exit of the last patient in the study? When was the blind broken to analyze the data?

I would appreciate hearing soon.

Thank again.

Best regards,

Len

301-594-5521

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

From: William Schary [mailto:wlschary@icnpharm.com]  
Sent: Thursday, January 06, 2005 6:16 AM  
To: KAPCALAL@cder.fda.gov  
Cc: Anil Hiteshi; Rory Turk; Kim Lamon  
Subject: Requested Responses

Good morning Dr. Kapcala,

Unfortunately, I have been away from the office, first over the holidays, and now in England, and I regret that I failed to provide a timely response to your question, and that my staff also did misinterpret your email of December 27. In response to your question of December 22 (Subject: Question regarding Zydis selegiline tyramine study), I offer the following response and chronology of events:

Following our initial discussions in August, I informed you that Valeant had placed the Tyramine study on hold, pending further input from the Division. Later following the communication from the Division that comments on the protocol would be considerably delayed (nothing expected before mid-September), Valeant reexamined the study design and objectives and after considering the ramifications of an extended delay, did decide to restart the delayed Selegiline Tyramine-Pressor Response study. That decision was made prior to our October 19, 2004 teleconference. This decision, although not mentioned in the teleconference, was previously disclosed in our submission of the revised SAP on November 24, 2004 (Serial No. 122). Regardless, many of the Division's comments and

recommendations regarding the study details and analyses were incorporated into both the revised SAP (version 2.0) and the final analysis at study completion. Please note that all changes to the SAP were made prior to the unblinding of the clinical study.

My understanding is that the SAP question responses are being finalized and will be forwarded to you later this week.

Please let me know if I can provide any further information on this chronology of events or on any other topic for that matter. I will return to the office next week.

Many thanks for your patience and consideration,

William L. Schary, PhD, RAC  
Vice President, Regulatory Affairs  
Valeant Pharmaceuticals International

(Tel) 714-427-6236 x4244  
(Fax) 714-641-7281  
(email) wlschary@valeant.com

## **Wheelous, Teresa A**

---

**From:** Anil Hiteshi [ahiteshi@valeant.com]  
**Sent:** Wednesday, January 12, 2005 7:07 PM  
**To:** Wheelous, Teresa A  
**Cc:** William Schary  
**Subject:** Re: NDA 21479 Zydys Selegiline Statistical Request for Additional Information

Hello Teresa,

In response to your request for additional information on the statistical clarification, we were able to locate your July 2, 2003 email to Donald Grilley at Elan.

It appears that there was a confusion with the definition of the data sets which was clarified in Elan's later submission.

Please let me know if you need anything further on this matter.

Thank you.

Kind regards,

Anil.

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

From: Wheelous, Teresa A [mailto:WHEELLOUST@cder.fda.gov]  
Sent: Wednesday, July 02, 2003 11:19 AM  
> To: 'Donald.Grilley@elan.com'  
> Subject: Statistical Clarification  
>  
> Don,

>  
> I contacted Dr. Jin about your statistical question and his reply is:  
>  
> Fanhui the reviewer says that this is no longer a issue. There was  
> a confusion with the definition of the data sets. The later submission  
> clarified it.  
>  
> CDR Teresa Wheelous, R. Ph.  
> Senior Regulatory Management Officer  
> Division of Neuropharmacological Drug Products  
> (301) 594-2850  
>  
> \*\*\*\*\*  
> This communication and any files transmitted with it  
> contain information which is confidential and may be privileged and  
> exempt from disclosure under applicable law. It is intended solely  
> for the use of the individual or entity to which it is addressed. If  
> you are not the intended recipient, you are hereby notified that  
> any use, dissemination or copying of this communication  
> is strictly prohibited. If you have received this  
> communication in error, please notify the sender.  
> Thank you for your co-operation.  
> \*\*\*\*\*

Thank you.

Anil.

-----  
Anil K. Hiteshi, R.A.C.  
Associate Director, Regulatory Affairs  
Valeant Pharmaceuticals International  
3300 Hyland Avenue  
Irvine, CA 92626  
Tel: (714) 545-0100, x3057  
Fax: (714) 641-7281  
ahiteshi@valeant.com

"Wheelous, Teresa  
A" To: "Anil Hiteshi  
(ahiteshi@icnpharm.com)" <ahiteshi@icnpharm.com>  
<WHEELOUST@cder.fda.gov> cc:  
Subject: NDA 21479 Zydys Selegiline  
Statistical Request for Additional Information

01/11/2005 09:12  
AM

Anil,

In the response to the approvable letter, reference is made to a July 2, 2003 email in which the Division agreed to the resolution of a statistical matter. Please provide detail information about the statistical matter in question, and how it was resolved. If you have copies of email communications about this matter it would further clarify your position.

Thank you,  
Teresa

## Wheelous, Teresa A

---

**From:** William Schary [wischary@icnpharm.com]  
**Sent:** Tuesday, January 11, 2005 8:30 PM  
**To:** KAPCALAL@cder.fda.gov  
**Cc:** teresa.wheelous@fda.hhs.gov; Kim Lamon; Anil Hiteshi; Rory Turk  
**Subject:** Response to the Dec 22 Question of Tyramine Study Chronology



FDA  
nse-Tyramine Study

Good morning Dr. Kapcala,

I apologize it has taken some time to respond to your questions but am providing a response at this time. Valeant does recognize and appreciate your interactions with us and we are attempting to provide responses that are direct and transparent as to our decisions and rationale behind them. In this particular case, as we have said previously, it would have been ideal to have realized that the study design needed to be changed prior to our meeting in May, so we could have discussed it with you at that time, but this was not the case. Consequently, due to the fact that we were informed that FDA feedback would be not before the middle of September, the Company made a business decision, based on what we saw as the scientific strength of the protocol, to resume enrollement in the trial. Since then, we have had discussions with you about this protocol initially in August until Dr. Katz presented the Division comments formally in our teleconference on October 19th. We considered those comments and have incorporated most of the key issues into the revised SAP and subsequent analyses and believe that the current analysis plan will address most all issues raised by the Agency in October. We regret the sequence of events but truly believe that we will be able to, in a scientifically sound manner, address all of the data you have requested.

I do hope that the following responses to your questions regarding the chronology of the study conduct and analysis of the data.

If I can be of further assistance in providing clarity to any other points, please contact me by email or telephone.

With regards,

William L. Schary, PhD, RAC  
Vice President, Regulatory Affairs  
Valeant Pharmaceuticals International

(see attached file: FDA response-Tyramine Study Chronology.doc)

## Wheelous, Teresa A

---

**From:** William Schary [wlschary@icnpharm.com]  
**Sent:** Tuesday, January 11, 2005 8:10 PM  
**To:** KAPCALAL@cder.fda.gov  
**Cc:** teresa.wheelous@fda.hhs.gov; Kim Lamon; Anil Hiteshi; Rory Turk; mpadams@SFBCI.com  
**Subject:** Responses to Requested information-Oct 8th Questions-stat questions



Bieck\_ref14.pdf  
(992 KB)



Response to  
Kapcala email of 0...

Hello Dr. Kapcala,

I am finally able to provide a complete response to your statistical questions from Oct. 8th. I can say that your questions on the statistical analysis of the tyramine protocol did elicit considerable rethinking and attention to our approach for analyzing this study. What I thought would be an easy and quick answer, ultimately ended up in significant activity and a revised SAP. We agree with you that our initial reference to the SAP as response to your questions is not the same as focused responses. As such, I was able to get our consultants to summarize the information into the following attached responses.

I do hope that this response is satisfactory, but if you do wish to comment further, or to discuss certain points with the consultants, we will assist in whatever way will provide you the answers you request.

Thanks again for your patience,

Best Regards,

William L. Schary, PhD, RAC  
Vice President, Regulatory Affairs  
Valeant Pharmaceuticals International

(Tel) 714-427-6236 x4244  
(Fax) 714-641-7281  
(email) wlschary@valeant.com

(See attached file: Bieck\_ref14.pdf) (See attached file: Response to Kapcala email of 08Oct2004 draft.doc)

**Wheelous, Teresa A**

---

**From:** Wheelous, Teresa A  
**Sent:** Tuesday, January 11, 2005 12:13 PM  
**To:** Anil Hiteshi (ahiteshi@icnpharm.com)  
**Subject:** NDA 21479 Zydys Selegiline Statistical Request for Additional Information

Anil,

In the response to the approvable letter, reference is made to a July 2, 2003 email in which the Division agreed to the resolution of a statistical matter. Please provide detail information about the statistical matter in question, and how it was resolved. If you have copies of email communications about this matter it would further clarify your position.

Thank you,  
Teresa

**Wheelous, Teresa A**

---

**From:** Wheelous, Teresa A  
**Sent:** Monday, January 10, 2005 2:36 PM  
**To:** Anil Hiteshi (ahiteshi@icnpharm.com)  
**Subject:** Request for desk copy of the Response to Approvable Letter Submission

Anil,

Our Clin Pharm Reviewer did not receive a copy of the response to the approvable letter for NDA 21-479. It was shredded by our document room while the reviewer was on leave. Since time is of the essence, would you provide me an electronic (email) copy of the Clin Pharm & Biopharm response sections to be used until you can send me desk copies of volumes 2 - 18 for her review?

Thank you,

*CDR Teresa Wheelous, R. Ph.  
Senior Regulatory Management Officer  
Office of Drug Evaluation I  
Division of Neuropharmacological Drug Products  
HFD-120  
1451 Rockville Pike  
Rockville, MD 20852  
Telephone (301) 594-5504  
Fax (301) 594-2859*

## Wheelous, Teresa A

---

**From:** Kapcala, Leonard P  
**Sent:** Tuesday, January 04, 2005 8:37 PM  
**To:** 'wlschary@icnpharm.com'; 'rturk@ribapharm.com'  
**Cc:** Kapcala, Leonard P; Wheelous, Teresa A  
**Subject:** RE: my question about your answer to my question of 12/22/04 e-mail

Hi Rory,

I think that you are misinterpreting what I was asking in this e-mail. I was not asking if Dr. Schary planned to answer my question in a single response with the requests of October 8 but whether I was eventually going to receive a response because I had not heard anything? For easy reference, I have cut and pasted the body of my December 22 e-mail just below my name.

The answer to my question ("Is this correct that all this was completed within 2 months or was this study ongoing up through the time that we had the teleconference on October 19?") seems to be a simple one. The answer to my question seems merely to be related to the date the study was completed.

I would appreciate an answer as soon as possible. I don't understand why there needs to be any delay in answering this simple question. I expected answers to my other requests (October 8) quite some time ago because I was given the impression back in October that the answers would be coming shortly.

Thank you.

Best regards,

Len

301-594-5521

Here is my e-mail from December 22.

Hi Dr. Schary,

I see that your response to approvable letter (NDA 21479, Zydis selegiline) was submitted on December 15. In August you had indicated that a few, or small number of subjects had already been enrolled/studied in the tyramine testing protocol (planning to enroll 80 subjects) but that Valeant was suspending the study until it could receive feedback from the DNDP. As you know we had a teleconference (October 19) discussing issues related to this protocol. At that time (10/19) we were under the impression that the tyramine study was still under suspension, that you were still awaiting our feedback before resuming this study, and that you would restart it after receiving our feedback.

If our understanding that this tyramine study was still under suspension (as of 10/19/04) was correct, then within two months (10/19-12/15), the majority of patients in the tyramine study would have been recruited, enrolled, completed participation in the study (study duration approximately three and a half weeks total), the data would have been collected and analyzed, and the final study report would have been written, and audited. Is this correct that all this was completed within 2 months or was this study ongoing up through the time that we had the teleconference on October 19?

Thank for this clarification.

Best regards,

Len

301-594-5521

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

From: Rory Turk [mailto:rturk@ribapharm.com]  
Sent: Tuesday, January 04, 2005 8:10 PM  
To: Kapcala, Leonard P  
Cc: Anil Hiteshi; William Schary  
Subject: RE: Redline version of Zelapar-Tyramine SAP

Dr. Kapcala-

You are correct. We intend to address the questions of the October 8 and Dec 22 email in a single response.

I apologize for the delayed reply.

Thank you,

Rory

<p>rturk@ribapharm.com&gt; &lt;KAPCALAL@cder.fda.gov&gt; Tyramine SAP</p>	<p>"Kapcala, Leonard P" &lt;KAPCALAL@cder.fda.gov&gt; a.gov&gt;</p>	<p>To: "'Rory Turk'" cc: "Kapcala, Leonard P" Subject: RE: Redline version of Zelapar-</p>
---	---	--

12/27/2004 10:13 AM

Thank you, Rory.

I assume that Dr. Schary will eventually answer my other question posed to him in my e-mail (Subject : "Question regarding Zydis selegiline tyramine study") sent to him on Wednesday, Dec 22? Is that correct?

Thanx.

Happy New Year!

Len Kapcala

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

From: Rory Turk [mailto:rturk@ribapharm.com]  
Sent: Monday, December 27, 2004 12:37 PM  
To: KAPCALAL@cder.fda.gov  
Cc: William Schary; Anil Hiteshi  
Subject: Redline version of Zelapar-Tyramine SAP

Dear Dr. Kapcala-

In response to your request, please find attached for your review, the 'red-line' version of the revised SAP (version 2.0) for the Zelapar-tyramine Phase 1 study. In this document, insertions to the original SAP (version 1.0) are presented in red and underlined, while deletions are presented as strikethrough text. Also attached is the summary of differences between the two versions. Both versions of the SAP and the summary of differences were submitted to the IND on November 24, 2004 (Serial No. 122). Please inform us if the 'red-line' version of the SAP should also be filed to the IND.

We continue to work with our CRO to address the outstanding questions regarding the SAP, originally posed in your October 8, 2004 email. Rest assured that the answers will be forthcoming as soon as they are made available to us.

Best wishes and happy holidays.

~~~~~  
Rory M. Turk, M.S.  
Regulatory Affairs Specialist  
Valeant Pharmaceuticals International  
3300 Hyland Ave  
Costa Mesa, CA 92626  
Tel 714.545.0100 x4042  
Fax 714.641.7281  
rurk@valeant.com

(See attached file: SAP Summary of Differences.doc) (See attached file: Tyramine SAP Redline 27Dec2004.doc)

## Wheelous, Teresa A

---

**From:** Ralph Carita [rjcarita@valeant.com]  
**Sent:** Friday, July 09, 2004 8:05 PM  
**To:** wheeloust@cdcr.fda.gov  
**Cc:** William Schary; Anil Hiteshi  
**Subject:** Zelapar Information Request IND-47,005



ZelaparTyramineCh...  
allengeStudy6...



Bieck\_ref.pdf (1  
MB)



Final QTc\_ECG  
protocol 060304...



Prasad\_ref.pdf  
(456 KB)



Redlined QTc\_ECG  
protocol 0603...



Redlined QTc\_ECG  
protocol 0629...



Zelapar QTc\_ECG  
Prot 062904.do...



Zelapar cover  
er.PDF (105 ...

Ms. Wheelous,

As per your emailed request to Dr. Schary dated 08-Aug-2004, I am forwarding Word format copies of the following documents;

1. QTc (ECG) protocol Amendment 1 (Final QTc\_ECG protocol 060304.doc)
2. Redline version of Amendment 1 (Redlined QTc\_ECG protocol 060304.doc)
3. QTc (ECG) protocol Amendment 2 (Zelapar QTc\_ECG Prot 062904.doc)
4. Redline version of Amendment 2 (Redlined QTc\_ECG protocol 062904.doc)
5. Tyramine challenge protocol (ZelaparTyramineChallengeStudy6-25-04\_Final.doc)

Below you will also find scans of the publications Dr. Schary cited in the cover letter of his submission dated 25-Jun-04.

6. Reference 1, Bieck et al (Bieck\_ref.pdf)
7. Reference 2, Prasad et al (Prasad\_ref.pdf)

This documentation was also included in the Protocol Amendment submission assigned serial number 118 and dated today 09-Jul-2004. A scan of this submissions cover letter is also attached to this email (Zelapar cover letter.pdf).

If there is any additional information or documentation we can provide, please feel free to ask.

Sincerely,

Ralph Carita  
Senior Regulatory Affairs Specialist  
Valeant Pharmaceuticals International  
Phone: 714-545-0100 x3356  
Fax: 714-641-7281

(See attached file: ZelaparTyramineChallengeStudy6-25-04\_Final.doc) (See attached file: Bieck\_ref.pdf) (See attached file: Final QTc\_ECG protocol 060304.doc) (See attached file: Prasad\_ref.pdf) (See attached file: Redlined QTc\_ECG protocol 060304.doc) (See attached file: Redlined QTc\_ECG protocol 062904.doc) (See attached file: Zelapar QTc\_ECG Prot 062904.doc) (See attached file: Zelapar cover letter.PDF)

## **Wheelous, Teresa A**

---

**From:** William Schary [wschary@icnpharm.com]  
**Sent:** Thursday, May 27, 2004 10:49 PM  
**To:** teresa.wheelous@fda.hhs.gov  
**Subject:** IND 47005 Zelapar New Protocol



Zelapar



SAP Protocol



Cover letter.doc  
(52 KB)



SN117\_fda-1571.d  
oc (86 KB)

xtocol\_051404\_final.NA600301.doc (48..

Good morning Ms. Wheelous,

I must apologize as I did believe the IND amendment had been submitted before our meeting Tuesday. As a courtesy, I am attaching the protocol and statistical analysis plan electronically. The package was submitted to the IND today.

I would like to ask a couple of questions regarding the tyramine study as we began considering the recommendations from the Division. I will be in contact next week. We

will be issuing an amendment incorporating the recommendations discussed at the meeting.

Sincerely,

William L. Schary, PhD, RAC  
Vice President, Regulatory Affairs  
Valeant Pharmaceuticals International

(Tel) 714-427-6236 x4244  
(Fax) 714-641-7281  
(email) wlschary@valeant.com

(See attached file: Zelapar Protocol\_051404\_final.doc) (See attached file: SAP Protocol  
RNA600301.doc) (See attached file: Cover letter.doc) (See attached file: SN117\_fda-1571.doc)

**Appears This Way  
On Original**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-479

VALEANT Pharmaceuticals International  
Attention: William L. Schary, Ph.D.  
3300 Hyland Avenue  
Costa Mesa, CA 92626

Dear Dr. Schary:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelapar (selegiline hydrochloride)

We also refer to your June 25, 2004, correspondence, received June 28, 2004, requesting a meeting to discuss the study design for a tyramine challenge study. We have considered your request and concluded that the meeting is unnecessary. However, in order to assist you in your drug development program, we recommend that you submit a complete and detailed protocol as a special protocol for review.

If you have any questions please call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at 301-594-2850

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Division Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/

-----  
Russell Katz  
7/13/04 09:28:39 AM

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-479

VALEANT PHARMACEUTICALS INTERNATIONAL

Attention: Edward F. Smith III, Ph.D.  
Director, Corporate Regulatory Affairs  
3300 Hyland Avenue  
Costa mesa, CA 92626

Dear Dr. Smith:

We acknowledge receipt on March 18, 2004, of your March 16, 2004, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: Zydis Selegiline (selegiline hydrochloride) Orally Disintegrating Tablet

NDA Number: 21-479

Name of New Applicant: Valeant Pharmaceuticals International

Name of Previous Applicant: Elan Pharmaceuticals Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Valeant Pharmaceuticals International as the sponsor of record for this application

All changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

NDA 21-479

Page 2

Address all communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

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

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

Sincerely,

*{See appended electronic signature page}*

Robbin Nighswander  
Supervisory Regulatory Health Officer  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Elan Pharmaceuticals, Inc.  
7475 Lusk Blvd.  
San Diego, CA 92121

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/

-----  
Robbin Nighswander  
4/5/04 01:32:35 PM

Appears This Way  
On Original

DEPARTMENT OF HEALTH AND  
HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**Clinical Pharmacology & Biopharmaceutics  
(HFD 860/870/880)  
Tracking/Action Sheet for Formal/Informal Consults**

From: Veneeta Tandon

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)  
Please log-in this consult and review action for the specified  
IND/NDA submission

DATE: 12/2/03

IND No.: N/A

NDA No. 21-479

DATE OF DOCUMENT  
1/15/03, 1/17/03, 8/7/03

NAME OF DRUG  
Zydis Selegiline (ZELAPAR)

PRIORITY CONSIDERATION

Date of informal/Formal  
Consult: 1/22/03, 1/27/03,  
8/19/03

NAME OF THE SPONSOR: [Elan Pharmaceuticals]

**TYPE OF SUBMISSION**

**CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE**

- |                                                  |                                                       |                                                                   |
|--------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------------------|
| <input type="checkbox"/> PRE-IND                 | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING                   |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES      | <input type="checkbox"/> LABELING REVISION                        |
| <input type="checkbox"/> IN-VITRO METABOLISM     | <input type="checkbox"/> IN-VIVO WAIVER REQUEST       | <input checked="" type="checkbox"/> CORRESPONDENCE                |
| <input type="checkbox"/> PROTOCOL                | <input type="checkbox"/> SUPAC RELATED                | <input type="checkbox"/> DRUG ADVERTISING                         |
| <input type="checkbox"/> PHASE II PROTOCOL       | <input type="checkbox"/> CMC RELATED                  | <input type="checkbox"/> ADVERSE REACTION REPORT                  |
| <input type="checkbox"/> PHASE III PROTOCOL      | <input type="checkbox"/> PROGRESS REPORT              | <input type="checkbox"/> ANNUAL REPORTS                           |
| <input type="checkbox"/> DOSING REGIMEN CONSULT  | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS    | <input type="checkbox"/> FAX SUBMISSION                           |
| <input type="checkbox"/> PK/PD- POPPK ISSUES     | <input type="checkbox"/> MEETING PACKAGE (EOP2)       | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> PHASE IV RELATED        |                                                       | [Tyramine Challenge Study 101 Re-Assessment, CYP P450 metabolism] |

**REVIEW ACTION**

- |                                                                                                         |                                                           |                                                        |
|---------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------------------------|
| <input checked="" type="checkbox"/> NAI (No action indicated)                                           | <input type="checkbox"/> Oral communication with          | <input type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to:                                                            | Name: [     ]                                             | <input type="checkbox"/> See comments below            |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox    | <input type="checkbox"/> Comments communicated in meeting | <input type="checkbox"/> See submission cover letter   |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others |                                                           | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| (Check as appropriate and attach e-mail)                                                                |                                                           |                                                        |

**REVIEW COMMENT(S)**

- NEED TO BE COMMUNICATED TO THE SPONSOR       NEEDS TO BE COMMUNICATED TO THE MEDICAL OFFICER

Two of these submissions were submitted very close to the action due date for N21-479 (1/29/03). The Reassessment of the Tyramine Challenge study 101 was submitted in response to the NA letter. The **sponsor's re-evaluation of study 101 was discussed internally** in the Clinical Division. The issues discussed pertained mainly to the clinical assessment of the study. The Office of Clinical Pharmacology and Biopharmaceutics did not have any additional comments to the study analysis.

Regarding the submission related to the request for literature search on CYP enzymes involved in the metabolism of selegiline, the **sponsor's response was not reviewed as it came in 2 days prior** to the action due date. On the face value the literature search did not seem comprehensive. This will be reviewed when the sponsor responds to the NA letter.

No actions are needed for these submissions at this time

|                                                 |                                                        |
|-------------------------------------------------|--------------------------------------------------------|
| SIGNATURE OF REVIEWER: <u>  Veneta Tandon  </u> | Date <u>  12/2/03  </u>                                |
| SIGNATURE OF TEAM LEADER: _____                 | Date _____                                             |
| CC.: HFD # [860]; TL: [Uppoor ]; DD: [Mehta]    | Project Manager: <u>  Teresa Wheelous  </u> Date _____ |

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/

-----  
Veneeta Tandon  
12/2/03 01:51:55 PM  
BIOPHARMACEUTICS

Ramana S. Uppoor  
12/2/03 02:02:32 PM  
BIOPHARMACEUTICS

Appears This Way  
On Original



**FACSIMILE TRANSMITTAL SHEET**

**DATE: August 4, 2003**

|                                                          |                                                                               |
|----------------------------------------------------------|-------------------------------------------------------------------------------|
| <b>To: Don Grilley</b>                                   | Teresa Wheelous                                                               |
| <b>Company: Elan</b>                                     | <b>From:</b><br>Division of Division of<br>Neuropharmacological Drug Products |
| <b>Fax number: 858) 558-4120</b>                         | <b>Fax number: (301 594-2859</b>                                              |
| <b>Phone number: (858) 457-7457</b>                      | <b>Phone number: (301) 594-2850</b>                                           |
| <b>Subject: NDA 21-479 Zydys Selegine DMETS Comments</b> |                                                                               |

**Total no. of pages including cover: 1**

Don,

The following are comments from the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety regarding the review of Zelapar:

**LABELING, PACKAGING AND SAFETY RELATED ISSUES**

DMETS has reviewed the container label and carton labeling of Zelapar and has identified the following areas of possible improvement, which might minimize potential user error.

**A. CONTAINER LABELS (blister packaging)**

The abbreviation "ODT" is not defined on the label. Although "ODT" is defined on the sachet and carton labeling, confusion may arise in the event that the blister packs are separated from the sachet and carton. Please avoid the use of this abbreviation without further clarification. Revise to read "Orally Disintegrating Tablet" rather than "ODT."

**B. CARTON LABELING (sample and trade unit pouch)**

1. The layout of section labeled "PATIENT'S INSTRUCTIONS FOR USE" is confusing as it is difficult to determine which numbered instruction corresponds with the pictures illustrated. For example, the instruction labeled "1. Peel back foil at the tab" appears in between two pictorials. At first glance, it is difficult to determine which pictorial the instructions correspond to. Please revise layout so that the instructions are closely and clearly associated with the respective pictorial.

2. The term "Zydis" in the statement "Zydis is a registered trademark of Cardinal Health, Inc." is not defined as done on the **side panel where it states "...in a Zydis orally disintegrating formulation."** Please delete the former statement or revise accordingly to clarify the meaning of "Zydis."

**C. PACKAGE INSERT LABELING**

Please submit for review.

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 594-2850. Thank you.**

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

/s/

-----  
Teresa Wheelous  
8/27/03 12:03:45 PM  
CSO

Appears This Way  
On Original

**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**(DMETS; HFD-420)**

**DATE RECEIVED:** 02/03/03

**DESIRED COMPLETION**

**ODS CONSULT #:** 02-0065-1

**DATE:** 7/28/03

**TO:** Russell Katz, M.D.  
Director, Division of Neuropharmacological Drug Products  
HFD-120

**THROUGH:** Teresa Wheelous  
Project Manager  
HFD-120

**PRODUCT NAME:**

**Zelapar**  
(Selegiline Hydrochloride)  
Orally Disintegrating Tablets  
1.25 mg

**NDA:** 21-479

**NDA SPONSOR:**

Elan Pharmaceuticals

**SAFETY EVALUATOR:** Alina R. Mahmud, R.Ph.

**SUMMARY:** In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), DMETS reviewed the proposed container label and carton labeling of Zelapar for possible interventions that may help minimize medication errors.

**RECOMMENDATIONS:**

1. DMETS recommends the implementation of the proposed labeling revisions outlined in section II of this review in order to minimize the potential for medication errors.
2. DMETS recommends that the proprietary name be submitted for a final review upon receipt of a response to the February 7, 2003 approvable letter from the sponsor. A re-review of the name 90 days prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names.

\_\_\_\_\_  
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; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**Label and Labeling Review**

**DATE OF REVIEW:** July 15, 2003

**NDA:** 21-479

**NAME OF DRUG:** **Zelapar**  
(Selegiline Hydrochloride)  
Orally Disintegrating Tablets  
1.25 mg

**NDA HOLDER:** Elan Pharmaceuticals, Inc.

**I. INTRODUCTION**

This consult is in response to a May 28, 2003 request by the Division of Neuropharmacological Drug Products to re-review the container label and carton labeling of Zelapar for possible interventions in minimizing medication errors.

At the time of the last review dated July 3, 2002, DMETS made several label and labeling recommendations. Additionally, the proprietary name Zelapar was found acceptable (see ODS consult 02-0065). This application received an approvable letter from the Division on February 7, 2003. The sponsor has not submitted a response to the approvable action.

**PRODUCT INFORMATION**

Zelapar contains the active ingredient selegiline hydrochloride. This product is seeking approval for an adjunctive treatment for the management of symptoms in patients with **Parkinson's disease that are exhibiting** deterioration of their response to levodopa/carbidopa therapy. Zelapar is available as a 1.25 mg selegiline hydrochloride orally dissolving tablet. Doses of 1.25 mg and 2.5 mg selegiline hydrochloride were effective as adjunctive therapy. The tablet(s) should be taken in the morning before breakfast and without liquid. ~~\_\_\_\_\_~~

~~\_\_\_\_\_~~Patients should also avoid ingesting food or liquids 5 minutes before or after taking Zelapar. The tablets are contained in a unit dose blister package with a foil backing.

b(4)

## II. LABELING, PACKAGING AND SAFETY RELATED ISSUES

DMETS has reviewed the container label and carton labeling of Zelapar and has identified the following areas of possible improvement, which might minimize potential user error.

### A. CONTAINER LABELS (blister packaging)

The abbreviation "ODT" is not defined on the label. Although "ODT" is defined on the sachet and carton labeling, confusion may arise in the event that the blister packs are separated from the sachet and carton. Please avoid the use of this abbreviation without further clarification. Revise to read "Orally Disintegrating Tablet" rather than "ODT."

### B. CARTON LABELING (sample and trade unit pouch)

1. The layout of section labeled "PATIENT'S INSTRUCTIONS FOR USE" is confusing as it is difficult to determine which numbered instruction corresponds with the pictures illustrated. For example, the instruction labeled "1. Peel back foil at the tab" appears in between two pictorials. At first glance, it is difficult to determine which pictorial the instructions correspond to. Please revise layout so that the instructions are closely and clearly associated with the respective pictorial.
2. The term "Zydis" in the statement "Zydis is a registered trademark of Cardinal Health, Inc." is not defined as done on the **side panel where it states "...in a Zydis orally disintegrating formulation."** Please delete the former statement or revise accordingly to clarify the meaning of "Zydis."

### C. PACKAGE INSERT LABELING

Please submit for review.

Appears This Way  
On Original

### III. RECOMMENDATIONS

- A. DMETS recommends the implementation of the labeling revisions outlined in section II of this review in order to prevent the potential for medication errors. In addition, we recommend that the package insert labeling be submitted for review.
- B. DMETS recommends that the proprietary name be submitted for a final review upon receipt of a response to the February 7, 2003 approvable letter from the sponsor. A re-review of the name 90 days prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names.

DMETS would appreciate feedback of the final outcome of this consult. 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, Project Manager, at 301-827-3242.

---

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

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/

-----  
Alina Mahmud  
7/31/03 01:13:57 PM  
PHARMACIST

Carol Holquist  
7/31/03 01:41:50 PM  
PHARMACIST

Jerry Phillips  
7/31/03 01:48:47 PM  
DIRECTOR

Appears This Way  
On Original



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

## FACSIMILE TRANSMITTAL SHEET

**DATE:** July 9, 2003

**To:** Don Grilley

Teresa Wheelous

**From:**

**Company:**

Division of Division of  
 Neuropharmacological Drug Products

**Fax number:** 858) 558-4120

**Fax number:** (301) 594-2859

**Phone number:** (858) 457-7457

**Phone number:** (301) 594-2850

**Subject:** NDA 21-479 Zydys Selegine Post Approvable Meeting Minutes

**Total no. of pages including cover:** 6

Don,

The following is a copy of the April 25, 2003 Meeting Minutes.

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 594-2850. Thank you.

Appears This Way  
 On Original

## MEETING MINUTES

**DATE:** April 25, 2003

**LOCATION:** WOC II conference Room E

**APPLICATION:** NDA 21-479 ZYDIS SELEGILINE

**TYPE:** Post Approvable Guidance Meeting

### ATTENDEES

#### FDA

| NAME                | TITLE & DIVISION                                                |
|---------------------|-----------------------------------------------------------------|
| Dr. Russell Katz    | Division Director HFD-120                                       |
| Dr. John Feeney     | Group Leader HFD - 120                                          |
| Dr. Leonard Kapcala | Medical Reviewer                                                |
| Dr. Barry Rosloff   | Pharmacology Team Leader HFD-120                                |
| Dr. Veneeta Tandon  | Clinical Pharmacology & Biopharmaceutics Team Leader<br>HFD-860 |
| Ms. Teresa Wheelous | Senior Regulatory Management Officer                            |

#### ELAN Pharmaceuticals REPRESENTATIVES

| NAME                     | TITLE                                       |
|--------------------------|---------------------------------------------|
| <b>Dr. Martin Koller</b> | V. P., Clinical Development North America   |
| Dr. Michael Scaife       | V. P., Global Regulatory Affairs            |
| Dr. Sue Griffith         | Sr. Director Clinical Development           |
| Dr. Chuck Davis          | Sr. Director Biostatistics                  |
| Mr. Donald Grilley       | Director Regulatory Affairs                 |
| Dr. Michael Weiss        | V. P., Medical & Scientific Affairs, Amarin |
|                          |                                             |

b(4)

### BACKGROUND:

In a submission dated February 17, 2003. Elan Pharmaceuticals requested a meeting to discuss the deficiencies detailed in the February 7, 2003 approvable letter. The meeting was granted on March 4, 2003 and the meeting package was received on April 7, 2003.

### DISCUSSION QUESTIONS:

#### CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

*Does FDA agree that a food-effect study is not needed for approval of this buccal form?*

- Tyramine Pressor Test questions were discussed along with the need to conduct a food study prior to approval.

- It was clarified that a food effect study was not asked for in the approval letter, but that the sponsor should verify the conduct of the study and explain the contradictory results obtained.
- Elan volunteered to conduct the food effect study again but without the Eldepryl arm. This approach was accepted at the meeting.

### **CLINICAL**

***Regarding the deficiencies noted in the February 7, 2003 Approvable letter, does FDA agree with Elan's proposal to investigate and provide responses to the issues of tyramine challenge response ratios, orthostatic vital signs and comprehensive ECG evaluation relative to tmax post-approval and that all other deficiencies / issues will be addressed in a complete response submission?***

- The sponsor reviewed various speculations about why results from study 101 might be spurious.
- Tyramine studies 007 & 014 are valid studies. However, by design, they do not provide all the desired safety information that was supposed to be derived from conducting study 101 (studies 007 & 014 used Eldepryl given as 10 mg once a day, not as the marketed regimen of 5 mg BID).
- If the sponsor thought that results from studies 007 and 014 were adequate for addressing DNDP's questions and potential concerns about possible MAO-A inhibition from Zydis selegiline (ZS), DNDP asked why the sponsor agreed to conduct study 101? It is DNDP's view that study 101 was conducted to address and answer questions that remained because of shortcomings from results of studies 007 and 014. Considering that results from study 101 are not easy to explain, it is difficult to dismiss them and rely on conclusions suggested by studies 007 and 014.
- The findings from tyramine challenge study 101 are difficult to understand. Study 101's results raised more questions than it answered. Although it is possible that results from study 101 are largely spurious for a variety of reasons, it is not possible to conclude whether they are or are not spurious. DNDP thinks that there are three major possibilities based upon results from study 101. First, neither Eldepryl nor ZS result in significant MAO-A inhibition. Second, both Eldepryl and ZS result in significant MAO-A inhibition. Third, only ZS causes a significant amount of MAO-A inhibition. DNDP thinks that it would be mainly speculative to conclude which of these 3 possibilities is correct. The best way to answer this question is by conducting a study that incorporates improvements in study design.
- Both the sponsor and DNDP agreed that the published literature does not provide significant information relative to the extent of MAO-A inhibition shown by oral tyramine testing after treatment with Eldepryl (5 mg BID) for approximately 2 weeks. The several publications in the literature show many important differences in study design to be able to provide comparable information relative to study 101.

- DNDP is in possession of seemingly reliable data (from proprietary sources) that cannot be shared, and that show that treatment with Eldepryl (5 mg BID) results in a tyramine sensitivity factor (TSF) ratio of approximately 2. In contrast, results from study 101 indicate a TSF ratio of almost 7 for both Eldepryl and the lowest dose of ZS (1.25 mg/d).
- Tyramine threshold responses in study 101 showed a significant percentage of patients who achieved a tyramine response at a dose of 25 mg or 50 mg in all dose groups but especially in the Eldepryl arm and the arm for the lowest dose of ZS (i.e. 1.25 mg/d). These results were clearly outliers compared to all results known in the literature and not published. The results from studies 007 and 014 also showed low percentages of patients exhibiting these tyramine threshold responses. DNDP could only find 2 patients (in the literature) who showed such responses suggesting that these occur very rarely. There were no such responses in patients evaluated in the proprietary study to which DNDP has access.
- The sponsor referred to the Zimmer et al. study (Acta Psychiatr Scand. Suppl 360: 81, 1990) in its written response and during the meeting and noted that one study in the literature showed a TSF of 5.4 for Eldepryl treatment. However, D. Kapcala noted that this study is of no real value because there are no details (? really TSF of 5.4, number of subjects, age, number of days treated with Eldepryl, dose of Eldepryl, number of patients with tyramine threshold responses to 25 mg or 50 mg of tyramine, criteria for tyramine threshold response) provided regarding the conduct of this study. These results appear to be proprietary in a Roche database.
- The TSF ratio discrepancy is a major problem and will require additional consideration by DNDP. The division will get back to the sponsor at a later date regarding its final thoughts on the TSF ratio discrepancy/concern.
- ~~\_\_\_\_\_~~
- Desired ECG data and orthostatic VS data could ideally be collected with respect to dosing in a repeat tyramine challenge study.
- The sponsor will review all available data sources to see if DNDP's concerns can be diminished regarding its concerns about possible MAO-A inhibition raised by results from study 101. More specifically, the sponsor was going to check to see if it could obtain placebo data (? from \_\_\_\_\_, showing the frequency of spontaneous variations of blood pressure and pulse that could be transient changes equivalent to threshold response for tyramine.
- The sponsor noted that there were no suggestions of QTc prolongation when data were reanalyzed and treatment differences were calculated for studies 25 and 26. However, after reviewing the QTc change from baseline tables provided under Tab F, it is apparent that there are mathematical errors (mainly in the sign but also in numerical calculation). When these errors are corrected, the corrected results support the division's original concern that ZS produces a treatment difference (i.e. QTc ZS - QTc placebo) for QTc change from baseline that ranges between approximately 5-8 msec QTc prolongation using all 3 QT correction formulae (i.e. "zero" slope, Bazett, and Fridericia). Thus, there is still a concern about QTc prolongation in a study conducted in which ECGs were not collected with respect to dosing. Conceivably, results could show greater QTc prolongation if ECGs were studied at certain times after dosing of ZS. The sponsor will notify DNDP if the corrections that DNDP made

b(4)

b(4)

regarding the sponsor's errors in presenting treatment differences (showing QTc prolongation) are not valid.

### **ACTION ITEMS**

1. The division will get back with Elan about the use of the tyramine challenge tests.
2. Elan will recalculate QT changes and get back to the division.

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/  
-----

Russell Katz

7/8/03 08:46:03 AM

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/

-----  
Teresa Wheelous  
7/9/03 02:28:18 PM  
CSO

Appears This Way  
On Original

## **MEMORANDUM**

**Date:** June 6, 2003

**From:** Fanhui Kong (HFD-710)

**To:** File NDA 21479 (Serial number 108)

**Subject:** Regarding the discrepancy between the sponsor and the statistical reviewer in the efficacy results of Study 025

The p-values for the treatment effect on the primary endpoint as the average of Weeks 10 to 12 given by the statistical reviewer and the sponsor differ for the LOCF analysis in Study 025. The reviewer gave a p-value of 0.127 while the sponsor gave 0.896.

Given the primary endpoint to be the average of the last two visits (Weeks 10 and 12), the agency and sponsor differ in the interpretation of LOCF imputation. If a patient is missing in at least one of these two visits, the sponsor took the last available visit as the LOCF imputation while the agency insisted that the average of the last TWO available visits be regarded as the LOCF imputation. The results of the first submission were based upon the sponsor's interpretation. In January of 2003's re-submission of the analysis, the sponsor adopted the agency's interpretation of LOCF imputation. Their analysis gave a p-value of 0.583 for the treatment effect for the primary endpoint.

In search for the reasons of such differences, the agency clarified the unclear description of the efficacy data set in the submission and upon which recreated the analysis data set. This gave a p-value of 0.555. The agency also found some small errors in the creation of the analysis data set by the sponsor for the second submission which led to a small discrepancy of 0.028 in p-value between theirs and ours.

**Cc:** Dr. Katz (HFD-120)  
Dr. Feeney (HFD-120)  
Dr. Kapcala (HFD-120)  
Ms. Wheelous, CSO (HFD-120)  
Dr. George Chi (HFD-710)  
Dr. Jin (HFD-710)

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/

Fanhui Kong  
6/9/03 04:43:10 PM  
BIOMETRICS

Appears This Way  
On Original