

**REQUEST FOR CONSULTATION**

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

FROM:

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
NAME OF DRUG		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE

NAME OF FIRM:

**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	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> 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:

PDUFA DATE:

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC:

Archival IND/NDA #####

HFD-###/Division File

HFD-###/RPM

HFD-###/Reviewers and Team Leaders

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

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Teresa Wheelous  
5/28/03 10:44:59 AM

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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: **4/25/03**

IND No.:

NDA No.  
**21-479**

DATE OF DOCUMENT  
**4/04/03**

NAME OF DRUG  
**Zydis Selegiline**

PRIORITY CONSIDERATION

Date of informal/Formal  
Consult **4/7/03**

NAME OF THE SPONSOR: **[Elan]**

**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 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        |   | [Approach to Response to NA letter]                        |

**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 checked="" 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

A sponsor meeting was held in response to the approvable letter. The sponsor had questions regarding the Tyramine Pressor Test and 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 they should verify the conduct of the study and explain the contradictory results obtained. The Sponsor volunteered to conduct the food effect study again but without the Eldepryl arm. Their approach was accepted at the meeting.

SIGNATURE OF REVIEWER: \_\_\_\_\_

Date 4/25/03

SIGNATURE OF TEAM LEADER: \_\_\_\_\_

Date \_\_\_\_\_

CC.: HFD # [860]; TL: [Uppoor ]; DD: [Mehta]

Project Manager: Lana Chen Date \_\_\_\_\_

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/s/

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Veneeta Tandon  
4/28/03 10:29:23 AM  
BIOPHARMACEUTICS

Ramana S. Uppoor  
4/28/03 10:46:29 AM  
BIOPHARMACEUTICS

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**MEETING MINUTES**

**DATE:** January 28,2003  
**LOCATION:** WOC II conference Room E  
**APPLICATION:** NDA 21-479 ZYDIS SELEGILINE FOR PARKINSON'S  
**TYPE:** Internal Status Meeting

**ATTENDEES**

**FDA**

**Dr. Russell Katz – Division Director**  
**Dr. John Feeney – Group Leader**  
**Dr. Leonard Kapcala – Medical Reviewer**  
**Dr. Kun Jin – Biometrics Team Leader**  
**Dr. Fanhui Kong – Biometrics Reviewer**  
**Dr. Ramana Upoor – Clinical Pharmacology & Biopharmaceutics Team Leader**  
**Dr. Vaneeta Tandon - Clinical Pharmacology & Biopharmaceutics Reviewer**  
**Teresa Wheelous – Project Manager**

**BACKGROUND:**

The user fee date for this original NDA is February 8, 2003, however, the sponsor continues to submit amendments to the application. Of particular interest is the January 10, 2003 submission, which provides a detailed statistical analysis of the primary endpoint. Ordinarily, these data are submitted at the time of the initial submission. The review team met to decide whether or not to consider this a major amendment causing the review clock to be extended by three months.

**DISCUSSION QUESTIONS:**

- A detailed statistical analysis of the primary and secondary endpoint was requested from the sponsor on several occasions beginning July 2002.
- While it may be possible to complete the review of this submission in roughly three weeks, the due date would occur prior to the completion of the review.
- Additionally, the tyramine challenge rebuttal, dated January 15, 2003, was received but did not provide any new or detailed data that adequately addresses the need to conduct another tyramine challenge study (as discussed in a telecon with the sponsor on October 24, 2002).
- The team decided to not review the statistical analysis submission during this review cycle and act on the application by the February 8, 2003 user fee date.

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/s/

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Russell Katz  
2/28/03 10:28:38 AM

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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: January 23, 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 Zydis October 24, 2002 Telecon Minutes**

**Total no. of pages including cover: 3**

Don,

The following is a copy of the official October 24, 2002 telecon minutes.

**Document to be mailed:**

YES

NO

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**MEMORANDUM OF TELECON****DATE:** October 24, 2002**APPLICATION NUMBER:** NDA 21-479 Zydis Selegiline for Parkinson's Disease**BETWEEN:**

Name: Lesley Groves, PhD, Project Manager  
Jaymin Shah, PhD, Biopharmaceutics  
Rose Kovelesky, PhD,  
Donald Grilley, Regulatory Affairs

\_\_\_\_\_ **b(4)**  
\_\_\_\_\_

Phone: 888-624-6186  
Representing: Elan Pharmaceuticals

**AND**

Name: Russell Katz, M.D., Division Director  
John Feeney, Group Leader  
Leonard Kapcala, Medical Reviewer  
Teresa Wheelous, Regulatory Management Officer  
Division of Neuropharmacological Drug Products, HFD-120

**SUBJECT:** To discuss the results and concerns of the most recently conducted tyramine challenge study.

**DISCUSSION:**

- The increased sensitivity to tyramine in the Eldepryl arm in study 101 seems to be at odds with results in the world's literature and results on file at the Agency. If these results from Elan's studies were correct, then we would need to address the seriousness of the tyramine-induced pressor effect for both Zydis selegiline and Eldepryl.
- A mean tyramine pressor ratio of 6.7 is reported in this study for Eldepryl 5 mg twice a day. This ratio is much higher than the expected ratio.
- Elan's most recent study also reports that there is no difference between the pressor effect of Eldepryl 5mg twice a day (mean tyramine pressor ratio of 6.7) and Zydis selegiline 1.25 mg (mean tyramine pressor ratio of 6.9), and therefore, there is no safety concern. However, these mean pressor tyramine pressor ratios are essentially identical and do suggest significant MAO-A inhibition, especially considering the number of subjects showing post treatment tyramine pressor dose of  $\leq 50$  mg. We are not aware of any experience suggesting such sensitivity to tyramine after Eldepryl treatment with 5 mg BID. If these results were true, exposure to a tyramine rich diet ranging between 10-50 mg of tyramine could result in serious hypertensive "cheese" reactions.
- If these results are accurate, then there is a safety concern for both Zydis selegiline and for Eldepryl. An explanation for these pressor effect results should be addressed.

- Because Elan's most recent trial did not incorporate a placebo arm and double-blinded conditions, we are not able to compare results of this trial adequately to assess the true extent of MAO-A inhibition from treatment.
- In the other tyramine challenge studies submitted in the NDA, the pressor effect ratios of a single dose of 10-mg Eldepryl range between 3.6 and 4.5. Because there were significant differences in the conduct of the three trials, a combined analysis of trials would not be acceptable.
- Conducting a double-blinded study with a placebo arm is the best recommendation for addressing the safety concerns generated by Elan's results.
- The sponsor would prefer to submit an argument for these apparently discrepant results instead of conducting another study.

### **ACTION ITEMS**

Elan can submit an argument explaining why DNDP should not be concerned about significant MAO-A inhibition suggested by Elan's results and the safety implications of these results. DNDP will consider any arguments put forth by Elan. However, DNDP thinks that it is unlikely that a compelling argument can adequately be made to dismiss the safety concerns stimulated by results from Elan's trials. DNDP prefers and recommends that Elan address the concerns of DNDP by conducting a new study incorporating a placebo arm in a double-blind trial.

Although not discussed in the telecon other possible considerations for a future study could include:

- 1) addition of also a higher ZS dose group of 10 mg to the other ZS doses of 1.25, 2.5 mg, and 5 mg to assess tyramine sensitivity across a wide range of doses in the same trial;
- 2) incorporating a positive control group involving treatment with a non-selective MAO inhibitor as a positive comparator for comparison with effects of ZS and Eldepryl in the same trial;
- 3) addition of a second control/pre-treatment oral tyramine testing to obtain an average control tyramine threshold dose for individuals and to provide for a more integrated, reliable baseline;
- 4) studying both males and females of older ages such as 40 – 70 years old (ages more closely resembling the population to be treated) instead of only young healthy males.

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/s/

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Teresa Wheelous  
1/23/03 03:35:16 PM  
CSO

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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** May 20, 2002

<b>To:</b> Don Grilley	Teresa Wheelous
<b>Company:</b>	<b>From:</b> Division of Division of Neuropharmacological Drug Products
<b>Fax number:</b> 858) 558-4120	<b>Fax number:</b> (301) 594-2859
<b>Phone number:</b> (858) 457-7457	<b>Phone number:</b> (301) 594-2850
<b>Subject:</b> NDA 21-479 Zydis Selegine Clinical Pharmacology & Biopharmaceutics Information Requests	

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

Don,

The NDA has been filed, however, the following information is requested:

- Please provide the study-specific analytical reports for the 8 PK studies (all except Study AN17933-101)
- Please provide a correct reference for the cross-study PK comparison with regard to old age that is included in the annotated label (It. 6/vol 15/p 1 does not contain this comparison).
- Please provide a cross-study PK comparison with regard to gender (Phase I studies in healthy subjects).
- Please update the annotated label for all references to Item 6, to reflect the volume/page numbers according to the overall NDA volume numbers given in volume 1, p 2-14.
- Please provide an extra desk copy of the combined report of Studies Z/SEL/97/025-026 including Appendix A-4 (PPK report). Please provide the data sets that were used for the NONMEM analysis electronically as SAS transport files.
- Please also include the control files used in the NONMEM analysis.
- Please provide data sets (as SAS transport files) for the pharmacokinetic parameters (individual values) with the corresponding subject demographics from the studies that the pharmacokinetic information in the label is based on.
- Please provide data sets (as SAS transport files) for the pharmacokinetic/pharmacodynamic data (individual values: plasma selegiline concentrations, and the pharmacodynamic variables vs. time) for Study AN17933-101
- If the sponsor would like to schedule a telecon to discuss the formats of the requested data sets with the OCPB reviewers, please contact Ms. Wheelous.

Please submit the requested reports/data

**Document to be mailed:**  YES  NO

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/s/

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Teresa Wheelous  
1/16/03 11:00:09 AM  
CSO

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NDA 21-479

Elan Pharmaceuticals, Inc  
Attention: Donald G. Grilley  
Director, Regulatory Affairs  
7475 Lusk Blvd.  
San Diego, CA 92121

Dear Mr. Grilley:

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

Name of Drug Product:                    Zydis (selegiline HCl)  
Review Priority Classification:        Standard (S)  
Date of Application:                    March 29, 2002  
Date of Receipt:                        April 8, 2002  
Our Reference Number:                NDA 21-479

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 8, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 8, 2002 and the secondary user fee goal date will be April 8, 2002.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application.

In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

U.S. Postal Service:

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

Courier/Overnight Mail:

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

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Teresa Wheelous (for) John S. Purvis

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>Clinical Pharmacology &amp; Biopharmaceutics</b> <b>(HFD 860/870/880)</b> <b>Tracking/Action Sheet for Formal/Informal Consults</b>		
From: <b>Ronald E. Kavanagh, BS Pharm, PharmD, PhD</b>		To: <b>DOCUMENT ROOM (LOG-IN and LOG-OUT)</b> Please log-in this consult and review action for the specified IND/NDA submission		
DATE: 8/27/02	IND No.: Serial No.:	NDA No. <b>21-479</b>	DATE OF THIS DOCUMENT	18 December 2002
NAME OF DRUG Zydis® Selegiline	PRIORITY CONSIDERATION <b>S or P</b>	Date of informal/Formal Consult:	8/27/02	
NAME OF THE SPONSOR: Elan				
<b>TYPE OF SUBMISSION</b> <b>CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS ASSIGNMENT</b>				
<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED				
<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)				
<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): [Pharmacodynamic Analysis]				
<b>REVIEW ACTION</b>				
<input type="checkbox"/> NAI (No action indicated)				
<input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)				
<input checked="" type="checkbox"/> Oral communication with Name: Len Kapcala, M.D. <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated:				
<input type="checkbox"/> Formal Review/Memo (attached) <input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>REVIEW COMMENT(S)</b>				
<input type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR				
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> 30 minute PD consult regarding tyramine pressor tests with MAO inhibitors.				
SIGNATURE OF REVIEWER: _____		Date _____		
SIGNATURE OF TEAM LEADER: _____		Date _____		
CC.: HFD # [120]; TL: [Baweja]; DD: [     ] CDR;		Project Manager: _____ Date _____		

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/s/  
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Ron Kavanagh  
12/18/02 04:16:28 PM  
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Raman Baweja  
12/18/02 05:13:24 PM  
BIOPHARMACEUTICS

Memo to file

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## MEMORANDUM OF TELECON

DATE: October 9, 2002

APPLICATION NUMBER: NDA 21-479, Zydys Selegiline

BETWEEN:

Name: Mr. Donald Grilley, Regulatory Affairs  
Phone: 858-457-7457  
Representing: Elan Pharmaceuticals

AND

Name: Teresa Wheelous, Regulatory Management Officer  
Dr. John Feeney, Group Leader  
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: (1) Reply to email sent regarding the requirements for distributing a placebo intended for promotional purposes, and (2) request a telecon to discuss the tyramine challenge study provided in the NDA.

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

**From:** Grilley, Donald [mailto:Donald.Grilley@elan.com]  
**Sent:** Thursday, September 26, 2002 6:01 PM  
**To:** Mona R' 'Zarifa (E-mail)  
**Subject:** Zelapar NDA 21-479

Hello, Mona,

I have a question regarding use of placebo Zelapar and what needs to be submitted to the NDA in regards to it.

We want to use placebo versions of the Zelapar orally disintegrating tablet for demonstration purposes to nursing homes, doctors, etc. to demonstrate how quickly the tablet disintegrates, taste, etc.

What do we need to provide under the NDA, if anything, to be able to distribute this placebo version of the product? Can we do something along the lines of simply labeling the individual tablets as Zelapar placebo for demonstration purposes only or such?

Thanks for your response,

Don

DISCUSSION:

Reply to Email Regarding Requirements for Distribution of a Placebo for Demonstration Purposes

- The sponsor is requested to send a letter to the NDA containing a request to use placebo for promotional purposes. This letter should cross reference the IND for CMC purposes.

- As for the label to be used on the placebo package, the language used should inform the user that the product does not contain an active ingredient and is for demonstration purposes only.
- These promotional materials should be sent for and advisory request to DDMAC.

Tyramine Challenge Studies

- Mr. Grilley agreed to a telecon to discuss the results of the tyramine challenge studies provided in the NDA. Of special concern is the trial conducted with 5mg of Eldepryl given twice a day as a control. This telecon will include an Elan clinical participant.

---

Dr. John Feeney  
Group Leader

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/s/

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Teresa Wheelous  
11/4/02 08:10:20 AM  
CSO

John Feeney  
11/4/02 09:22:52 AM  
MEDICAL OFFICER  
concur

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**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** October 7, 2002

**APPLICATION:** NDA 21-479 Zydys Selegiline

**TYPE OF MEETING:** Safety – Tyramine Challenge Studies

**MEETING CHAIR:** Dr. Russell Katz

**MEETING RECORDER:** CDR Teresa Wheelous

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>HFD#</u>
1. Dr. Russell Katz	Division Director	HFD-120
2. Dr. John Feeney	Group Leader	HFD-120
3. Dr. Barry Rosloff	Pharmacology Team Leader	HFD-120
4. Dr. Lois Freed	Pharmacology Reviewer	HFD-120
5. Dr. Ramana Uppoor	Clinical Pharmacology & Biopharmaceutics Team Leader	HFD-860
6. Dr. Veneeta Tandon	Clinical Pharmacology & Biopharmaceutics Reviewer	HFD-860
7. CDR Teresa Wheelous	Project Manager	HFD-120

**BACKGROUND:**

In this NDA are the results of a tyramine challenge study, which incorporated an Eldepryl 5 bid arm. The results for the Eldepryl arm are at odds with the world's literature in that they suggest that Eldepryl may inhibit MAO-A and increase sensitivity to tyramine by a factor of 6 or more. In one sense, the results for the Eldepryl arm are "too good to be true" since they make the Zydys arms look no worse than Eldepryl. In another sense, the results might seem bad because they suggest that the marketed Eldepryl may NOT selective and might put some patients at risk for the Cheese reaction.

**MEETING OBJECTIVES:**

Decide what should be done to confirm the results of this study.

**DISCUSSION POINTS:**

- Based upon the data available in literature articles, the degree of increase in blood pressure reflected in the data collected from this trial is unexpected. A minimal increase in blood pressure with Selegiline 5mg orally twice a day is expected.

- The results of this study show Zydis selegiline at 1.25mg dose as being equivalent in pressor effect as oral selegiline 5mg twice a day.
- Confirmation that the data is robust to support a significant pressor effect with selegiline 5mg twice a day.
- The sponsor should be informed of our concern and requested to provide a justification for these unexpected results while addressing the difference in pressor results from the previous tyramine challenge study.

**ACTION ITEMS:**

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
1. Gather additional data from all tyramine challenge studies in preparation for a telecon with the sponsor.	Medical Reviewer	Telecon date
2. Consider site inspection.		
3. Arrange telecon with sponsor	Project Manager	ASAP

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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: October 7, 2002**

<b>To: Don Grilley</b>	Teresa Wheelous
<b>Company:</b>	<b>From:</b> Division of Division of 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 Statistical Information Requests</b>	

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

Don,

The following are statistical comments regarding the Zydys Selegiline NDA:

1. You should submit ITT LOCF analysis data set for the primary efficacy endpoints for Z/SEL/97/026 and Z/SEL/97/025 separately.
2. Present the statistical analysis results for the ITT LOCF data set for the primary efficacy endpoint and other efficacy endpoints for studies Z/SEL/97/026 and Z/SEL/97/025 separately and for the combined data from both studies, as were expected based upon interactions with the DNDP and the written documents.
3. Analyze the ITT OC dataset appropriately for the primary efficacy endpoint by including only subjects with diary data from baseline, week 10, and week 12 for studies Z/SEL/97/026 and Z/SEL/97/025 separately and for combined data from both studies.
4. Present an analysis of the primary efficacy endpoint and other efficacy endpoints for the ITT completer dataset according to the statistical analysis plan.

Thanks,  
Teresa

**Document to be mailed:**  YES  NO

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/s/

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Teresa Wheelous  
10/7/02 09:49:57 AM  
CSO

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# MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration

Date: October 4, 2002

From: Fanhui Kong, Ph.D.  
Statistical Reviewer

Subject: **Recommendations Regarding Statistical Analysis Issues and Concerns for NDA 21479 (Zydis selegiline)**

To: Russell Katz, M.D.  
Division Director, DNDP  
John Feeney, M.D.  
Neurology Team Leader, DNDP  
Kun Jin, Ph.D.  
Statistical Team Leader, DNDP

According to the memo by Dr. Kapkala on September 18, I would like to send this request of further analysis to the sponsor.

Some issues regarding planned statistical analyses are not always clearly specified in the various written documents. We believe that:

1. The sponsor has not presented the appropriate analyses of the ITT LOCF datasets (for studies Z/SEL/97/026 and Z/SEL/97/025 separately and these studies combined) for the primary efficacy endpoint and other efficacy endpoints as were expected based upon interactions with the DNDP and the written records.
2. The sponsor has not conducted an appropriate analysis of the primary efficacy endpoint for the ITT observed case datasets for studies Z/SEL/97/026 and Z/SEL/97/025 separately and for these studies combined. Patients should be included in this analysis only when there are available data for percentage reduction from baseline for "OFF" from both the week 10 and 12 timepoints that can be averaged.
3. The sponsor did not analyze the ITT OC dataset appropriately for the primary efficacy endpoint by including only subjects with diary data from baseline, week 10, and week 12.
4. The sponsor has not presented an analysis of the primary efficacy endpoint and other efficacy endpoints for the ITT completer dataset as was supposed to be done according to the statistical analysis plan.

Therefore here are the things that we recommend the sponsor to do:

1. The sponsor should submit ITT LOCF analysis data set for the primary efficacy endpoints for Z/SEL/97/026 and Z/SEL/97/025 separately.
2. The sponsor should present the statistical analysis results for the ITT LOCF data set for the primary efficacy endpoint and other efficacy endpoints for studies Z/SEL/97/026 and Z/SEL/97/025 separately and for the combined data from both studies, as were expected based upon interactions with the DNDP and the written documents.
3. The sponsor should analyze the ITT OC dataset appropriately for the primary efficacy endpoint by including only subjects with diary data from baseline, week 10, and week 12 for studies Z/SEL/97/026 and Z/SEL/97/025 separately and for combined data from both studies.
4. The sponsor should present an analysis of the primary efficacy endpoint and other efficacy endpoints for the ITT completer dataset according to the statistical analysis plan.

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**Wheelous, Teresa A**

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**From:** Kapcala, Leonard P  
**Sent:** Thursday, September 19, 2002 11:41 AM  
**To:** Katz, Russell G; Feeney III, John J; Jin, Kun; Kong, Fanhui; Wheelous, Teresa A  
**Subject:** Zydis selegiline statistical issues prompting request for additional efficacy analyses for NDA 21479

Gang,  
FYI. Fanhui and I have identified some important statistical efficiencies in the efficacy analyses and have jointly drafted a memo outlining the problems and our conclusions. Fanhui will draft a letter to the sponsor requestng the desired analyses.

Len



ZSND21479Statistica  
Analysisl...

7-29-02

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September 5, 2002

**Summary of Discussion (between Fanui Kong and Len Kapcala) of Statistical Analysis Issues for NDA 21479 (Zydis selegiline)**

During the review of this NDA, questions were raised as to whether the sponsor has conducted the primary efficacy analysis as pre-specified and in accordance with expectations and recommendations by DNDP. Questions regarding primary efficacy analyses were raised at a 7/29/02 teleconference with the sponsor and appropriate representatives of the sponsor. The sponsor has recently responded with clarifications and answers to questions raised at the teleconference. This meeting was held to assess the adequacy of the sponsor's primary efficacy analysis.

- The sponsor's original protocols for phase 3, pivotal trials (studies Z/SEL/97/026 and Z/SEL/97/025) noted that the primary efficacy analysis would be conducted on the ITT patient population using the LOCF convention, thus the ITT-LOCF dataset. Specific wording on page 26 of the protocol noted : "The primary population for analysis of efficacy variables is defined as the intention-to-treat last observation carried forward (LOCF) dataset." The ITT population was defined as patients who were randomized to a treatment, received at least 1 dose of study medication, had baseline percent "OFF" time data collected, and had at least one set of "OFF" time data collected during treatment.
- Protocol amendment # 2 (2/4/98) noted that the primary efficacy analysis was changed to analyze the ITT population instead of the LOCF dataset. Specific wording on page 26 noted : "The primary population for analysis of efficacy variables is defined as the intention-to-treat population." This amendment further noted that a detailed plan of analysis would be prepared before the randomization codes is broken and the analysis of the trial results begins.
- DNDP faxed (10/15/99) comments to the sponsor regarding the sponsor's statistical analysis plan for studies Z/SEL/97/026 and Z/SEL/97/025. DNDP pointed out that the ITT population should be included in the primary efficacy analysis and analyses of secondary efficacy variables. The fax further noted that "We recommend that the LOCF method be used for missing data when applicable."
- On 12/10/99 the sponsor (Elan) submitted a revised statistical analysis plan along with responses to DNDP comments communicated to the sponsor on 10/15/99. The sponsor provided the following response to DNDP's recommendation (i.e. that the primary efficacy analysis and efficacy analyses of secondary variables utilize the ITT-LOCF dataset).

"The ITT population will be changed to include all patients who have been randomized and have received at least one dose of study drug. Please note that this will result on a combined analysis of patients receiving 1.25 and 2.5 mg doses. Such an analysis was previously planned to be secondary in nature.

This change has been incorporated into Section 3.1 on page 12."

- Section 3.1 of the statistical analysis plan describes analysis populations and the analysis strategy. The **primary efficacy analysis** is that performed on the primary efficacy parameter and considering an 'Intent-to-Treat' population (see LOCF-ITT population definition below) consisting of patients who were randomized, received at least one dose of study medication and completed a subsequent evaluation visit. Other efficacy analyses are described following definitions for the various patient populations considered."

The LOCF ITT population is described in section 3.1 as follows. "The term "**LOCF ITT Population**" will be used to refer to the ITT population in which the LOCF principal (sic) has been used in handling missing data. (LOCF is applied when data are missing from a post baseline time interval but exist in a preceding on-study-medication time interval. LOCF will be applied to time slotted data)."

Toward the end of section 3.1 there is further mention of the LOCF ITT population and various efficacy analyses. "**Additional efficacy analyses** are performed on the primary efficacy parameter considering the ITT completers population (with no imputation of missing data so that analyses are on the ITT completer only), the LOCF ITT population, and the PP population. All secondary efficacy analysis parameters are analyzed on the ITT completers population, the LOCF ITT population, and the PP population."

- During the 7/29/02 teleconference the sponsor was asked "whether or not observed cases (OC) or Last Observation Carried Forward (LOCF) datasets were used in the efficacy analyses." The response further noted that the ITT population was defined in the analysis database that was used for the primary efficacy analysis. LOCF algorithms were implemented in the programming for data tables and were used to perform an additional (secondary) efficacy analyses.

According to the final study report (for study Z/SEL/97/026, the only "**positive pivotal trial**") contained within the NDA, efficacy analyses were performed on the observed case (OC) data at each timepoint for all efficacy parameters and analysis of this dataset appeared to be the primary efficacy analysis. Although neither the protocol nor statistical analysis plan specified that the OC ITT would be part of the primary efficacy analysis, the protocol did note that one of the datasets to be analyzed would be the "visit-wise" dataset in which valid observations at each visit would be analyzed. However, it is not clear if the OC ITT is the same as the "visit-wise" dataset. Furthermore, the statistical analysis plan did not mention nor describe an observed case or visit-wise dataset.

- jjjol

- hjk
  
- for missing LOCF dataset would be one of the datasets analyzed for the ITT patients. Other datasets to be analyzed included the visit-wise dataset, the completer dataset, and the per protocol dataset. Amendment # 4 (2/4/98) revised the protocol so that the primary population for primary efficacy analysis would be changed from the ITT LOCF population to the ITT population.

The ITT population was defined as patients who were randomized to a treatment, received at least 1 dose of study medication, had baseline percent "OFF" time data during waking hours, and had at least one set of "OFF" time data during treatment. Amendment # 2 (2/4/98) noted that the primary efficacy analysis was changed to analyze the ITT population instead of the LOCF dataset. However, the Statistical Analysis Plan (12/9/99) noted that the primary efficacy analysis would be performed on the ITT population and refers to the reader to "(see LOCF ITT population definition below)."

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**FACSIMILE TRANSMITTAL SHEET**

**DATE:** August 1, 2002

<b>To:</b> Don Grilley	Teresa Wheelous
<b>Company:</b>	<b>From:</b> Division of Division of Neuropharmacological Drug Products
<b>Fax number:</b> (858) 558-2549 <i>don's work</i> 4120	<b>Fax number:</b> (301) 594-2859
<b>Phone number:</b> (858) 457-7457	<b>Phone number:</b> (301) 594-2850
<b>Subject:</b> NDA 21-479 Zydys Selegine Non-compliant structure – Electronic Document Room & QT document format recommendation	

**Total no. of pages including cover:** 3

The above referenced electronic submission contained the following problems:

**Non-compliant structure**

Did not contain files in .pdf format

No TOC was provided

No electronic 356h provided

Invalid/Compressed SAS .xpt files

**Other** - Files in .ctl and csv. format

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## Division of Neuropharmacological Drug Products Recommendations for QT interval correction

QT interval length decreases with increasing heart rate. Use of a method of adjusting the QT interval length for heart rate allows the QT interval length to be considered independent of the heart rate at which it was observed.

Direct adjustment of the QT interval for heart rate by dividing the QT length by the square root of the RR interval ( $QTc^{SR} = QT/RR^{.5}$ ), a method first proposed by Bazett in 1920 and the one most commonly used today, clearly results in substantial bias. For heart rates greater than 60, the  $QTc^{SR}$  overcorrects the QT interval whereas it undercorrects for rates less than 60. Hence, when exploring the  $QTc^{SR}$  data for a drug that increases the heart rate, there would appear to be a dose dependency for the  $QTc^{SR}$  even if the drug had no effect on cardiac repolarization. At the same time, correction with Bazett's method could mask QT interval prolongation with a drug that causes bradycardia.

The potential bias from using the square root adjustment has been well described in the literature with many authors proposing alternative methods of adjustment. The cube root correction ( $QTc^{CR} = QT/RR^{.33}$ ), first proposed by Fridericia, can also produce a systematic bias, but the degree of bias is much smaller than Bazett's method and goes in the opposite direction. Both biases appear to be independent of age.

Since Bazett's correction, or  $QTc^{SR} = QT/RR^{.5}$ , greatly overcorrects for rates greater than 60 and Fridericia's correction, or  $QTc^{CR} = QT/RR^{.33}$ , slightly undercorrects, we have explored corrections that use slightly larger fractional exponents than 1/3. As it turns out, the model,  $QTc = QT/RR^{.37}$ , fits most datasets fairly well with only a small degree of bias in any one dataset. If one chooses to use this method of correction, we would recommend using the fractional exponent that produces a line with a zero slope in the placebo/baseline data to adjust the on-study QT data.

This method includes the following steps for each exponent tested:

1. Correct the placebo/baseline QT data with the exponent
2. Plot the corrected QT values (using that exponent) against the RR length
3. Calculate the regression line and determine its slope

The exponent generating the slope closest to zero would be selected.

In 1992, Sagie proposed an alternative method for correction after describing the flaws with Bazett's method. We have extended his approach of linear model based correction to randomized studies by fitting a linear model of  $QT = a + b \times RR$  to the placebo/unexposed (baseline) study population to adjust the on-study drug group. Using this estimated slope "b", one could then standardize the data for both drug and control treatment groups to a normalized heart rate of 60 bpm (beats per minute) using the following equation:

$$\text{observed QT(in msec)} + [\text{slope} ( (1-RR))] = \text{standardized QT.}$$

One would then proceed with comparing the drug and control experiences. In the 7 datasets that we have examined, this approach worked well.

Since the apparent shape of the QT/heart rate relationship is nonlinear, more complicated models that use nonlinear regression have also been proposed. However, these approaches require sophisticated regression programs and seem to offer little improvement in fit from adjustment based upon a linear model or the fractional exponent method described above.

To summarize, we recommend one of two correction methods be used:

1. identification of the fractional exponent "X" in  $QT/RR^{-X}$  that produces a 0 slope with the corrected placebo and/or baseline data plotted against RR
2. the linear model based correction

If you have questions regarding these methods, please contact the Division.

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**FACSIMILE TRANSMITTAL SHEET**

**DATE:** July 15, 2002

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

**Total no. of pages including cover:** 2

Don,

The following are comments from the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety regarding the review of the proposed name Zelapar: DMETS has no objections to the use of the proprietary name, "Zelapar". DMETS has reviewed the container label, carton labeling, and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. We have identified areas of improvement, in the interest of minimizing potential user error and patient safety.

DMETS recommends consulting Dan Boring of the USAN council and the Labeling and Nomenclature Committee for the proper designation of the dosage form. The sponsor has labeled their product as an "Orally Dissolving Tablet". DMETS questions whether the designation of "Orally Disintegrating Tablet" may be more appropriate for this dosage form.

A. Container Label (foil blister packaging)

1. Increase the prominence of the proprietary and established names.
2. Prominently include the product strength in direct association with the proprietary and established names.
3. Decrease the prominence of the company name/logo.

B. Carton Labeling (pouch sample packaging)

1. See comment A2 and A3.
2. Increase the prominence of the established name.
3. Relocate the "Each Zelapar tablet contains 1.25 mg selegiline hydrochloride in a Zydis fast-dissolving formulation" statement to the side panel.



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END=MAY-20 13:05

FILE NO. = 185

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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: May 20, 2002**

<b>To: Don Grilley</b>	<b>From:</b> Teresa Wheelous
<b>Company:</b>	Division of Division of Neuropharmacological Drug Products
<b>Fax number: 858) 558-4120</b>	<b>Fax number:</b> (301) 594-2859
<b>Phone number: (858) 457-7457</b>	<b>Phone number:</b> (301) 594-2850
<b>Subject: NDA 21-479 Zydis Selegine Clinical Pharmacology &amp; Biopharmaceutics Information Requests</b>	
<b>Total no. of pages including cover: 1</b>	

Don,

The NDA has been filed, however, the following information is requested:

- Please provide the study-specific analytical reports for the 8 PK studies (all except Study AN17933-101)
- Please provide a correct reference for the cross-study PK comparison with regard to old age that is included in the annotated label (It. 6/vol 15/p 1 does not contain this comparison).
- Please provide a cross-study PK comparison with regard to gender (Phase I studies in healthy subjects).
- Please update the annotated label for all references to Item 6, to reflect the volume/page numbers according to the overall NDA volume numbers given in volume 1, p 2-14.
- Please provide an extra desk copy of the combined report of Studies Z/SEL/97/025-026 including Appendix A-4 (PPK report). Please provide the data sets that were used for the NONMEM analysis electronically as SAS transport files.
- Please also include the control files used in the NONMEM analysis.
- Please provide data sets (as SAS transport files) for the pharmacokinetic parameters (individual values) with the corresponding subject demographics from the studies that the pharmacokinetic information in the label is based on.
- Please provide data sets (as SAS transport files) for the pharmacokinetic/pharmacodynamic data (individual values: plasma selegiline concentrations, and the pharmacodynamic variables vs. time) for Study AN17933-101
- If the sponsor would like to schedule a telecon to discuss the formats of the requested data sets with the OCPB reviewers, please contact Ms. Wheelous.

Please submit the requested reports/data

**Document to be mailed:**

YES

NO

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## MEETING MINUTES

**DATE:** May 15, 2002

**TIME:** 2 PM

**LOCATION:** WOC II conference Room E

**APPLICATION:** NDA 21-479

**TYPE:** RTF Meeting

### ATTENDEES

Dr. R. Katz – Division Director  
Dr. J. Feeney – Group Leader  
Dr. L. Kapcala – Medical Reviewer  
Dr. B. Rosloff – Pharmacology Team Leader  
Dr. L. Freed – Pharmacology Reviewer  
Dr. M. Guzewska – CMC Team Leader  
Dr. M. Zarifa – CMC Reviewer  
Dr. F. Chen – Statistics Reviewer  
Dr. K. Jin - Statistics Team Leader  
Dr. M. Sunzel – Clinical Pharmacology & Biopharmaceutics  
Dr. R. Uppoor - Clinical Pharmacology & Biopharmaceutics Team Leader

### DISCUSSION:

#### CMC

- This application is fileable.

#### PHARMACOLOGY

- This application is fileable.
- The sponsor submitted a 1-month oral mucosal irritation study in hamster and a TK bridging study in dog. The sponsor had been asked to conduct the 1-month irritation study and to provide justification for using oral studies to support the Zydis formulation. It will be a matter of review whether or not the sponsor has adequately justified the use of the oral studies to support the new formulation.

#### CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

- This application is fileable
- A bioequivalence study was conducted with the 1.25 mg formulation. The AUC and  $C_{max}$  are almost double that of the reference product.
- There is a labeling concern in regards to the directions for usage. \_\_\_\_\_

b(4)

- There are several information requests that should be forwarded to the sponsor.

### **STATISTICS**

- This application is fileable

### **CLINICAL**

- This application is fileable despite several concerns of not submitting some data as requested at the last pre-NDA meeting.
- Patient diaries contain several different categories (e.g. "on", "on" with dyskinesias, "off", asleep) for classifying a patient's status over 24 hours. However, data from only one category (e.g. "off") appears to be presented in the application. It would be important to know how Zydis selegiline may have altered the time and % time in all categories. Presentation and analyses of these data for all categories should be requested.
- There are several information requests that should be forwarded to the sponsor.

### **ACTION ITEM**

- This application is fileable.
- Since this is a standard application with a 10-month review clock, the PDUFA date is February 8, 2003.

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NDA 21-479

Elan Pharmaceuticals, Inc  
Attention: Donald G. Grilley  
Director, Regulatory Affairs  
7475 Lusk Blvd.  
San Diego, CA 92121

Dear Mr. Grilley:

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

Name of Drug Product: Zydis (selegiline HCl)  
Review Priority Classification: Standard (S)  
Date of Application: March 29, 2002  
Date of Receipt: April 8, 2002  
Our Reference Number: NDA 21-479

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 8, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 8, 2002 and the secondary user fee goal date will be April 8, 2002.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

U.S. Postal Service:

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

Courier/Overnight Mail:

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

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

Sincerely,

*{See appended electronic signature page}*

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

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FILE NO. = 144

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**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS (HFD-120)**  
 5600 FISHERS LANE  
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PLEASE DELIVER THE FOLLOWING PAGE(S) TO:

DONALD GRILLET  
DIRECTOR, REG AFFAIRS

FAX # 858 558 4120  
 FROM: 4120

TERESA WHEELER

*X10A*

*21-479*

*RE LETTER*

*& LABELING*

*858 558 1448*

Total number of pages, including cover page: 22

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START=FEB-07 16:49

END=FEB-07 16:56

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## MEETING MINUTES

**DATE:** January 28, 2003

**LOCATION:** WOC II conference Room E

**APPLICATION:** NDA 21-479 ZYDIS SELEGILINE FOR PARKINSON'S

**TYPE:** Internal Status Meeting

### ATTENDEES

#### FDA

**Dr. Russell Katz – Division Director**  
**Dr. John Feeney – Group Leader**  
**Dr. Leonard Kapcala – Medical Reviewer**  
**Dr. Kun Jin – Biometrics Team Leader**  
**Dr. Fanhui Kong – Biometrics Reviewer**  
**Dr. Ramana Uppoor – Clinical Pharmacology & Biopharmaceutics Team Leader**  
**Dr. Vaneeta Tandon - Clinical Pharmacology & Biopharmaceutics Reviewer**  
**Teresa Wheelous – Project Manager**

### BACKGROUND:

The user fee date for this original NDA is February 8, 2003, however, the sponsor continues to submit amendments to the application. Of particular interest is the January 10, 2003 submission, which provides a detailed statistical analysis of the primary endpoint. Ordinarily, these data are submitted at the time of the initial submission. The review team met to decide whether or not to consider this a major amendment causing the review clock to be extended by three months.

### DISCUSSION QUESTIONS:

- A detailed statistical analysis of the primary and secondary endpoint was requested from the sponsor on several occasions beginning July 2002.
- While it may be possible to complete the review of this submission in roughly three weeks. The due date would occur prior to the completion of the review.
- Additionally, the tyramine challenge rebuttal, dated January 15, 2003, was received but did not provide any new or detailed data that adequately addresses the need to conduct another tyramine challenge study (as discussed in a telecon with the sponsor on October 24, 2002).
- The team decided to not review the statistical analysis submission during this review cycle and act on the application by the February 8, 2003 user fee date.

**MEMORANDUM OF TELECON****DATE:** October 24, 2002**APPLICATION NUMBER:** NDA 21-479 **Zydis Selegiline for Parkinson's Disease****BETWEEN:**

**Name:** Lesley Groves, PhD, Project Manager  
Jaymin Shah, PhD, Biopharmaceutics  
Rose Kovelesky, PhD,  
Donald Grilley, Regulatory Affairs

\_\_\_\_\_

\_\_\_\_\_ **b(4)**

**Phone:** 888-624-6186  
**Representing:** Elan Pharmaceuticals

**AND**

**Name:** Russell Katz, M.D., Division Director  
John Feeney, Group Leader  
Leonard Kapcala, Medical Reviewer  
Teresa Wheelous, Regulatory Management Officer  
Division of Neuropharmacological Drug Products, HFD-120

**SUBJECT:** To discuss the results and concerns of the most recently conducted tyramine challenge study.

**DISCUSSION:**

- The increased sensitivity to tyramine in the Eldepryl arm in study 101 seems to be at odds with results in the world's literature and results on file at the Agency. If these results from Elan's studies were correct, then we would need to address the seriousness of the tyramine-induced pressor effect for both Zydis selegiline and Eldepryl.
- A mean tyramine pressor ratio of 6.7 is reported in this study for Eldepryl 5 mg twice a day. This ratio is much higher than the expected ratio.
- Elan's most recent study also reports that there is no difference between the pressor effect of Eldepryl 5mg twice a day (mean tyramine pressor ratio of 6.7) and Zydis selegiline 1.25 mg (mean tyramine pressor ratio of 6.9), and therefore, there is no safety concern. However, these mean pressor tyramine pressor ratios are essentially identical and do suggest significant MAO-A inhibition, especially considering the number of subjects showing post treatment tyramine pressor dose of  $\leq 50$  mg. We are not aware of any experience suggesting such sensitivity to tyramine after Eldepryl treatment with 5 mg BID. If these results were true, exposure to a tyramine rich diet ranging between 10-50 mg of tyramine could result in serious hypertensive "cheese" reactions.
- If these results are accurate, then there is a safety concern for both Zydis selegiline and for Eldepryl. An explanation for these pressor effect results should be addressed.

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- **Because Elan's most recent trial did not incorporate a placebo arm and double-blinded conditions, we are not able to compare results of this trial adequately to assess the true extent of MAO-A inhibition from treatment.**
- In the other tyramine challenge studies submitted in the NDA, the pressor effect ratios of a single dose of 10-mg Eldepryl range between 3.6 and 4.5. Because there were significant differences in the conduct of the three trials, a combined analysis of trials would not be acceptable.
- Conducting a double-blinded study with a placebo arm is the best recommendation for **addressing the safety concerns generated by Elan's results.**
- The sponsor would prefer to submit an argument for these apparently discrepant results instead of conducting another study.

#### **ACTION ITEMS**

Elan can submit an argument explaining why DNDP should not be concerned about significant **MAO-A inhibition suggested by Elan's results and the safety implications of these results.** DNDP will consider any arguments put forth by Elan. However, DNDP thinks that it is unlikely that a compelling argument can adequately be made to dismiss the safety concerns stimulated by **results from Elan's trials. DNDP prefers and recommends that Elan address the concerns of DNDP by conducting a new study incorporating a placebo arm in a double-blind trial.**

Although not discussed in the telecon other possible considerations for a future study could include:

- 1) addition of also a higher ZS dose group of 10 mg to the other ZS doses of 1.25, 2.5 mg, and 5 mg to assess tyramine sensitivity across a wide range of doses in the same trial;
- 2) incorporating a positive control group involving treatment with a non-selective MAO inhibitor as a positive comparator for comparison with effects of ZS and Eldepryl in the same trial;
- 3) addition of a second control/pre-treatment oral tyramine testing to obtain an average control tyramine threshold dose for individuals and to provide for a more integrated, reliable baseline;
- 4) **studying both males and females of older ages such as 40 – 70 years old (ages more closely resembling the population to be treated) instead of only young healthy males.**

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Center for Drug Evaluation and Research  
Office of Drug Evaluation I

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** August 1, 2002

<b>To:</b> Don Grilley	Teresa Wheelous
	<b>From:</b>
<b>Company:</b>	Division of Division of Neuropharmacological Drug Products
<b>Fax number:</b> (858) 558-2549	<b>Fax number:</b> (301) 594-2859
<b>Phone number:</b> (858) 457-7457	<b>Phone number:</b> (301) 594-2850
<b>Subject:</b> NDA 21-479 Zydys Selegine Non-compliant structure – Electronic Document Room & QT document format recommendation	

**Total no. of pages including cover:** 3

The above referenced electronic submission contained the following problems:

**Non-compliant structure**

- Did not contain files in .pdf format
- No TOC was provided
- No electronic 356h provided
- Invalid/Compressed SAS .xpt files
- Other** - Files in .ctl and csv. format

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Office of Drug Evaluation I

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** July 15, 2002

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

**Total no. of pages including cover:** 2

Don,

The following are comments from the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety regarding the review of the proposed name Zelapar: **DMETS has no objections to the use of the proprietary name, "Zelapar".** DMETS has reviewed the container label, carton labeling, and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. We have identified areas of improvement, in the interest of minimizing potential user error and patient safety.

DMETS recommends consulting Dan Boring of the USAN council and the Labeling and Nomenclature Committee for the proper designation of the dosage form. The sponsor **has labeled their product as an "Orally Dissolving Tablet". DMETS questions whether the designation of "Orally Disintegrating Tablet" may be more appropriate for this dosage form.**

A. Container Label (foil blister packaging)

1. Increase the prominence of the proprietary and established names.
2. Prominently include the product strength in direct association with the proprietary and established names.
3. Decrease the prominence of the company name/logo.

B. Carton Labeling (pouch sample packaging)

1. See comment A2 and A3.
2. Increase the prominence of the established name.
3. **Relocate the "Each Zelapar tablet contains 1.25 mg selegiline hydrochloride in a Zydys fast-dissolving formulation" statement to the side panel.**

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4. A statement should be included as to whether or not the pouch sample packaging is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed outpatient, it should be in a child-resistant container. For example: This sample carton is not child resistant.

C. Carton Labeling (sample and trade unit carton packaging)

1. See comments B1-B4.

2. The sample unit carton packaging contains the wording "~~\_\_\_\_\_~~". The phrase "~~\_\_\_\_\_~~" is redundant and could lead to confusion. Remove the "~~\_\_\_\_\_~~" phrase on the sample unit carton packaging.

b(4)

D. Package Insert Labeling

1. In the "How Supplied" section the first sentence reads "~~\_\_\_\_\_~~". The salt, hydrochloride, should be included with this statement to read "~~\_\_\_\_\_~~" to properly represent the product strength.

b(4)

2. The abbreviation "ODT" is used very prominent through out the insert labeling. Revise the insert to include the actual wording, Orally Dissolving Tablets. Please note the designation "dissolving" may not be the proper USAN term. This term may be requested to be changed based on the recommendations from the consult with Dan Boring of the USAN council and the Labeling and Nomenclature Committee.

3. The "How Supplied" section reads, "~~\_\_\_\_\_~~". Labeling was only provided for the product to be packaged in cartons. There is also no reference that the carton is child-resistant. Revise the word "~~\_\_\_\_\_~~" to "carton" and see comment B4.

b(4)

4. The "Storage" section reads "~~\_\_\_\_\_~~". This statement is confusing since each tablet is individually sealed in a blister unit. Provide additional information for a healthcare professional and patient to understand the significance and reason for this statement.

b(4)

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## MEETING MINUTES

**DATE:** May 15, 2002

**TIME:** 2 PM

**LOCATION:** WOC II conference Room E

**APPLICATION:** NDA 21-479

**TYPE:** RTF Meeting

### ATTENDEES

Dr. R. Katz – Division Director  
Dr. J. Feeney – Group Leader  
Dr. L. Kapcala – Medical Reviewer  
Dr. B. Rosloff – Pharmacology Team Leader  
Dr. L. Freed – Pharmacology Reviewer  
Dr. M. Guzewska – CMC Team Leader  
Dr. M. Zarifa – CMC Reviewer  
Dr. F. Chen – Statistics Reviewer  
Dr. K. Jin - Statistics Team Leader  
Dr. M. Sunzel – Clinical Pharmacology & Biopharmaceutics  
Dr. R. Uppoor - Clinical Pharmacology & Biopharmaceutics Team Leader

### DISCUSSION:

#### CMC

- This application is fileable.

#### PHARMACOLOGY

- This application is fileable.
- The sponsor submitted a 1-month oral mucosal irritation study in hamster and a TK bridging study in dog. The sponsor had been asked to conduct the 1-month irritation study and to provide justification for using oral studies to support the Zydis formulation. It will be a matter of review whether or not the sponsor has adequately justified the use of the oral studies to support the new formulation.

#### CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

- This application is fileable
- A bioequivalence study was conducted with the 1.25 mg formulation. The AUC and  $C_{max}$  are almost double that of the reference product.
- There is a labeling concern in regards to the directions for usage. Patients are instructed not to swallow for 2 minutes after dose administration.

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- There are several information requests that should be forwarded to the sponsor.

### **STATISTICS**

- This application is fileable

### **CLINICAL**

- This application is fileable despite several concerns of not submitting some data as requested at the last pre-NDA meeting.
- **Patient diaries contain several different categories (e.g. "on", "on" with dyskinesias, "off", asleep) for classifying a patient's status over 24 hours. However, data from only one category (e.g. "off") appears to be presented in the application. It would be important to know how Zydis selegiline may have altered the time and % time in all categories. Presentation and analyses of these data for all categories should be requested.**
- There are several information requests that should be forwarded to the sponsor.

### **ACTION ITEM**

- This application is fileable.
- Since this is a standard application with a 10-month review clock, the PDUFA date is February 8, 2003.

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**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** November 7, 2001

**TIME:** 2:30 PM

**LOCATION:** WOC 2 Conference Room E

**APPLICATION:** IND 47,005 Zydys Selegiline HCL

**TYPE OF MEETING:** Pre-NDA

**MEETING CHAIR:** Dr. Russell Katz

**MEETING RECORDER:** Ms. Teresa Wheelous

**FDA ATTENDEES, TITLES**

1. Dr. Russell Katz – Division Director
2. Dr. John Feeney – Group Leader
3. Dr. Leonard Kapcala – Medical Reviewer
4. Dr. Barry Rosloff – Pharmacology Team Leader
5. Dr. Lois Freed – Pharmacology Reviewer
6. Dr. Iftekar Mahmood – Clinical Pharmacology & Biopharmaceutics Reviewer
7. Dr. Judith Racoosin – Safety Team Leader
8. Dr. Sharon Yan – Biometrics Reviewer
9. Ms. Teresa Wheelous – Regulatory Management Officer

**ELAN PHARMACEUTICALS ATTENDEES**

1. ~~\_\_\_\_\_~~
2. ~~\_\_\_\_\_~~
3. Ms. Michele Fajardo, Associate Director, Document Control
4. ~~\_\_\_\_\_~~
5. Dr. Jaymin Shah, Director, Clinical Pharmacology and Clinical Pharmacokinetics,
6. Dr. Kent Shellenberger, Vice President, Clinical Affairs, Elan
7. Dr. George Shopp, Senior Scientist, Safety Evaluation, Elan
8. ~~\_\_\_\_\_~~

b(4)

b(4)

**BACKGROUND:**

The original IND 47,005 was submitted by Scherer DDS on December 30, 1994, and in a submission dated February 10, 1999, the agency was notified that Elan Pharma International Limited became the new sponsor of this IND.

Pre-NDA meetings were held with Scherer DDS on July 11, 1996 and with Elan Pharmaceuticals on January 30, 2001.

**MEETING OBJECTIVES:**

1. Identify any major unresolved issues.
2. Obtain a waiver of pediatric studies.
3. Present general information to be submitted in the NDA including the proposed draft labeling and the formatting of data.
4. Discuss whether the proposed statistical analyses of the ISE and the ISS are satisfactory.

**DISCUSSION POINTS:**

1. **Are our statistical plans for the ISE and the ISS acceptable? (please refer to Section 7, Attachment D, P. 062 and Attachment E, P. 095 .)**

**Efficacy**

Although not directly related to the ISE the following was discussed at the meeting.

Dr. Katz asked if Elan was interested in claiming the efficacy of both 1.25 mg and 2.5 mg and how it was specified in the protocol.

Elan responded that efficacy for 1.25 mg was not planned in the protocol. The protocol specified endpoint was Weeks 10 to 12 for 2.5 mg, but it would be instructive to look at the first 6 weeks for the efficacy of 1.25 mg. \_\_\_\_\_ from Elan said that the efficacy results were found to be positive even with a conservative adjustment. b(4)

Dr. Yan from FDA pointed out that an appropriate study design to compare 1.25 mg and 2.5 mg with placebo would be a 3-parallel-group study that has independent patients receiving 1.25 mg or 2.5 mg. In this study the same patients received both 1.25 mg and 2.5 mg. Furthermore, the analysis was post-hoc. Even though the difference between the 1.25 mg group and placebo is statistically significant, the results might not be valid.

Dr. Katz said that Elan can present the data and results and we will look at them.

**Safety****Safety Requests**

Attachment E: ISS statistical analysis plan

**1.0 Treatment groupings**

- ◇ Study 008 should not be pooled with 025 and 026 because it was open-label (i.e. not blinded)

**2.2 Safety Evaluations**

- ◇ Are SAEs just treatment emergent (TE)? DNDP wants TE SAEs and AEs not total SAEs and AEs. Should also provide breakdown of # TE SAEs/patient and #TE AEs/patient.

#### 4.4 Analysis of safety data

- ◇ study 008 should not be pooled with 025/026
- ◇ are deaths included in SAEs?
- ◇ In all the summary tables for the “randomized parallel studies”, doses 1.25 and 2.5 are grouped together; did they explore differences in TEAEs between these doses?
- ◇ 4.4.1 extent of exposure- need a person-years estimate by treatment group and study; or we can calculate it if they provide number of patients exposed for days 1-7; 8-14; 15-30; 31-60; 61-90; etc
- ◇ 4.4.2 AEs- TE SAE or AE should be reported for up to 30 day after last dose (or at least 7)
  - ◇ table 4.1.6: frequency of AEs at 1.25 and 2.5 broken out just for selected (commonly occurring?) preferred terms?
  - ◇ Table 4.1.2 (and others) sorted by descending frequency of the overall count? Is that within each body system?
  - ◇ TE SAEs and AEs should be presented irregardless of assessed causal relationship to study drug and also as a breakdown according to assessed relationship. In addition (at a minimum), these data should be presented as a binary categorization defining "related" if assessed as "possibly, probably or definitely related" and "not-related" if assessed as "not-related, unrelated, or unlikely related"; a more detailed breakdown of all these categories is also acceptable
- ◇ 4.4.3 Labs: was there a central lab? What is the difference between potentially clinically important, clinically significant, and substantially abnormal values?
  - ◇ The breakdown into relatively mild abnormal categories (e.g.  $< \text{LLN}$ ,  $\leq 0.9 \times \text{LLN}$  AND  $\leq 0.75 \times \text{LLN}$  may be too fine to have much clinical utility). At the MOST, the breakdown in abnormal laboratory results should not be  $> 3$  categories including abnormal (any result outside of reference range such as  $< \text{LLN}$ ), potentially clinically important (or analogous term to represent some more, severe abnormality you define such as  $< 0.75 \times \text{LLN}$ ), and perhaps "panic" value to represent a very severe, potentially life-threatening abnormality such as an absolute neutrophil count  $< 500$ , total platelet count  $< 25,000$ , serum potassium  $\leq 2.5$  or  $\geq 6.5$ , or serum sodium  $\leq 120$  or  $\geq 160$  that you define.
  - ◇ Please add absolute neutrophil count to your hematology parameters.
  - ◇ Provide outlier tables based on substantially abnormal values (p. 103) considering only patients who were normal at baseline
- ◇ 4.4.4 oral exams- specific criteria to follow? were abnormal patches biopsied?
- ◇ 4.4.5 Vital signs- need mean (N, SD, min, max, med) absolute value data and change from baseline according to treatment group; DNDP wants analysis of orthostatic changes; as it stands supine, sitting, and standing are all analyzed separately but it does not appear that sponsor is analyzing data for changes of orthostatic VS (i.e. supine, sitting, and standing systolic and diastolic blood pressure and pulse).
- ◇ 4.4.6 ECGs – centrally read manually under blinded conditions or just machine read? need definitions of clinically significant changes; need mean change from

baseline and outlier analyses for intervals (especially QTc) duration. Need analyses to show N, mean, SD, min, max, median for absolute values and change from baseline over time and for Maximal change from baseline over time according to treatment group. Sponsor should follow DNDP recommendations for QTc analyses.

- ◇ QTc data analyzed by \_\_\_\_\_ only for study 026. Study 025 just analyzed categorically. Considering the relatively small amount of QTc data analyzed from the sponsor's study, the sponsor should supplement its analyses by summarizing QTc and ECG results/data from the literature and post-marketing experience with selegiline
- ◇ Can the data listings be submitted electronically?
  - ◇ Are AE data listings treatment emergent? Most important are SAEs, AEs leading to D/C from study.
  - ◇ Where are the narratives? Narratives are needed
  - ◇ Appendix 2
    - ◇ Absolute neutrophil count should be provided (p. 109) along with other hematology values
    - ◇ VS-oral temperature (> 39 degrees C) would be better to consider potentially clinical important ( NOT > 40 degrees C)

b(4)

**2. Has Elan adequately characterized and quantified the safety profile of Zydis selegiline over a reasonable duration of time consistent with the intended long-term use of this drug? (refer to Section 6.3)**

Yes. The total number of patients exposed for  $\geq 6$  months is 276 and the total number exposed for  $\geq 12$  months is 238. These exposures are acceptable.

**3. Is the preclinical package sufficient for an NDA; especially the dog and hamster studies? (refer to Section 9)**

The TK study in dog and the buccal study in hamsters have not been reviewed in detail. In addition to the nonclinical data provided to date, the sponsor should submit a summary of PK/TK data in the nonclinical toxicity species [including rat and mouse] and humans. The human data should include plasma exposures at the maximum proposed clinical dose. These data are needed in order to justify using the oral toxicity studies to support the buccal formulation.

**3. 4. Is the format for the proposed NDA acceptable? (refer to Section 11, and Attachment C, P. 053 .)**

Yes

5. **Is our request for a full pediatric waiver acceptable? (refer to Section 4.5 and Attachment C, P. 053 )**

Yes

6. **Is our plan adequate for providing financial disclosure? (refer to Attachment F, P. 230.)**

Yes. When a financial disclosure is not provided for a PI or sub PI the sponsor needs to show the due diligence that was put forth and clearly explain what was attempted, what happened, and why there is no financial disclosure for specific individuals. However, DNDP needs to clarify whether financial disclosure is needed for study coordinators and will inform the sponsor.

7. **Are our plans for providing an electronic submission of items 11 and 12 of the NDA acceptable? (refer to Section 8)**

Yes

8. **Do you have any comments or suggestion at this time concerning the draft package insert? (see Attachment A, P. 032)**

No. The language in the package insert will depend on the results of the review of the NDA.

**Clinical Pharmacology/Biopharmaceutical Issues**

- The sponsor needs to address how plasma Cmax and AUC of parent and metabolites of this new product relates to PK parameters of immediate release product.
- The sponsor needs to address how 1.25 mg/day and 2.5 mg/day doses bracket the immediate release 10 mg/day product.
- The sponsor was asked about their dissolution plan and they responded that dissolution studies have already been conducted for the Zydys formulation.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

## Meeting Minutes

**Meeting Date:** January 30, 2001  
**IND:** 47,005  
**Drug:** Zydis Selegiline  
**Sponsor:** Elan Pharmaceuticals  
**Type of Meeting:** Pre-NDA Meeting (Clinical)

**Participants:** see attached.

**Meeting Objective:**

1. Provide an overview of the clinical and biopharmaceutical information proposed to be submitted in support of a 505(b)(2) NDA.
2. Solicit comments and advice.

**Discussion Points (bullets):**

- The attached sponsor meeting minutes appear accurate, except for the following points, and will otherwise serve as official minutes.

**PLEASE LIST EXCEPTIONAL POINTS HERE**

1. Dissolution data for Zydis Selegiline should be submitted.

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Signature, minutes preparer

Concurrence Chair

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Teresa Wheelous, R.Ph.  
Regulatory Project Manager, DNDP

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Russell Katz, M.D.  
Division Director, DNDP

Attachment – sponsor minutes

5 February 2001  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug Products  
Woodmont Two Building 4<sup>th</sup> Floor  
HFM-99, Room 200N  
1451 Rockville Pike  
Rockville, MD 20852-1448

**Attn.: Russell G. Katz, M.D.**

**Director, Division of Neuropharmacological Drug Products  
HFD-120**

**RE: Zydis<sup>®</sup> Selegiline HCl  
IND 47,005  
Serial No. 085**

**General Correspondence: Elan Minutes to Meeting of 30 January**

Dear Dr. Katz:

Please refer to the Clinical/Biopharmaceutics pre-NDA meeting conducted on the 30<sup>th</sup> of January, 2001, regarding Zydis selegiline, between representatives of Elan Pharmaceuticals, Inc. and the Agency. We also wish to convey our appreciation for the time you and your team spent to discuss the information presented.

At this time we are providing Elan's minutes for this meeting, which reflect our understanding of the discussions. We would appreciate receiving a copy of the official FDA meeting summary and/or a confirmation that the minutes being presented here are in concurrence with FDA's viewpoint of these discussions.

Please contact me at (650) 877-7497 or (800) 435-5108 should there be any questions. Alternatively, I may be reached by facsimile at (650) 616-5053.

Sincerely,

Michael R. Johnston  
Manager, Regulatory Affairs

Elan Pharmaceuticals, Inc.

Clinical / Biopharmaceutics Pre-NDA Meeting

Zydis Selegiline HCl: IND 47,005

30 January 2001

Attendees

Elan:

Dr. D. Canafax	Director, Clinical Affairs
Mr. M. Johnston	Manager, Regulatory Affairs
Dr. C. Robinson	Vice President, Project Management
Dr. J. Shah	Director, Clinical Pharmacology
Dr. M. Scaife	Vice President, Regulatory Affairs
Dr. K. Shellenberger	Vice President, Clinical Affairs

Elan Consultants:

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FDA:

Dr. J. Feeney	Group Leader
Dr. K. Jin	Biometrics Team Leader
Dr. R. Katz	Division Director, DNDP
Dr. I. Mahmood	Biopharmaceutics Reviewer
Ms. T. Wheelous	Project Manager
Dr. S. Yan	Biometrics Reviewer

## Summary

Based on the data presented by Elan, FDA concurred that a Section 505(b)(2) NDA filing for Zydis® selegiline using one positive efficacy study, provided that it was statistically robust, (Z/SEL/97/026) in combination with the other supportive studies for safety and other required information supportive for this type of submission was acceptable for filing and had the potential for marketing approval.

Regarding the statistical analysis for both effectiveness studies (025 and 026), the FDA requested: follow the statistical analysis plan as previously agreed upon and confirm robustness of Study 026 by assessing normalcy of the primary endpoint. If the data are not normally distributed, then perform a nonparametric analysis as described in the statistical analysis plan. Following the meeting, the FDA faxed details of the format that the statistical reviewer wanted for the data presented (see attached). Additionally, the FDA was interested in reviewing the analysis of the combined data from the two studies, which still provided a statistically significant result for the primary endpoint.

Elan agreed to conduct and provide data from an oral tyramine challenge study (PK/PD) with Zydis selegiline 2.5 mg compared to 5 mg bid commercial dosage form at steady state. This study was recommended to compare any potential MAO-A inhibition from Zydis selegiline (2.5 mg) and the approved commercial dosage form at doses used clinically.

Additionally, a breakdown of the adverse event “stomatitis” would be provided, since all the verbatim terms that were collapsed in this one were not actually stomatitis. The FDA agreed to this presentation of these data.

The FDA inquired about the timing for filing the NDA. Dr. Shellenberger replied that it would be in approximately eight months.

## Detailed Minutes

### **Introduction**

Dr. Scaife presented an introduction of the participants, meeting objectives, agenda and regulatory history. The meeting was convened in order to present the clinical and

biopharmaceutical data which would be supportive of a Section 505(b)(2) NDA filing for the Zydis selegiline dosage form of selegiline hydrochloride. Of particular interest to Elan was the question of whether, given the rationale, body of effectiveness/safety data, and use of one positive study (Z/SEL/97/026) and one supportive study (Z/SEL/97/025), the FDA would find this to be adequate to support an NDA filing.

Dr. Katz asked if the approval in Europe was based upon the data presented in the clinical studies in this meeting. Dr. Scaife explained that the approvals in Europe were based on PK/PD data and a switch study (008), with no additional clinical studies being required. Dr. Scaife continued by presenting the proposed Zydis selegiline indication statement, which was verbatim from the Eldepryl<sup>®</sup> package insert. Dr. Scaife reviewed the rationale for this dosage form and for selegiline in general as an adjunct to levodopa/carbidopa therapy for Parkinsonian patients.

#### ***PK/PD Data***

Dr. Shellenberger then presented summary PK and PD information on the Zydis selegiline 1.25, 2.5 and 10mg data collected as well as that for the standard tablet form of 10 mg. This included comparisons of AUC (ng\*hr/ml), Cmax (ng/mL) and 24 hour urine PEA excretion (µg). The conclusion was that Zydis selegiline, in the range of 1.25 to 2.5 mgs, brackets the 10-mg dose of the conventional tablet form for these variables both at single dose and at steady state.

#### ***Clinical Studies / Effectiveness Results***

The study design (identical for 025 and 026) was then presented by Dr. Shellenberger. A comment was made by \_\_\_\_\_ regarding the patient population tested being more severe than those patients who would ordinarily receive treatment. These patients were experiencing an average of 7 hours of “off time” during waking hours, which is considerably more than the average patient who would begin this therapy. When the study results were presented, Dr. Katz asked a number of questions about the statistical analysis of the data and the robustness of the study (026) findings in light of the suggested placebo effect seen in Study 025. \_\_\_\_\_ gave a detailed reply to these questions assuring the group that the findings in 026 were robust. \_\_\_\_\_ agreed that the analysis could include a non-parametric approach in addition to the parametric

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primary analysis. The statistical analysis plan did include this provision if the parametric assumptions had not been met and was followed as previously agreed.

In presenting the secondary endpoints, Dr. Katz queried Dr. Shellenberger on the methodology for determining the evaluation on the "Global Impression of Improvement" by the investigators. \_\_\_\_\_ explained the methodology as outlined in the protocol. Elan agreed to clarify exactly how the measurements were taken; for example, did the evaluating clinicians have records back to the beginning for each evaluation or only to the last examination? b(4)

In reviewing the results of the two studies, Dr. Katz asked how the 13% reduction in off time compared to data from Eldepryl studies submitted to the FDA. Elan responded we could not present this comparison as these data had not been published and were not in the package insert. \_\_\_\_\_ then pointed out that a reduction of "off" time of even an hour and a half would be significant for these patients. He went on to point out that a "PPG" study in which he was involved as an investigator, demonstrated a reduction in off time of 1.3 hours as the primary outcome, and this drug was approved with that reduction. Additionally, Dr. Katz asked that Elan provide their "case" in the NDA regarding the aberrance for Study 025 in combination with the demonstration of robustness of Study 026. Dr. Katz also asked why Elan had conducted the two studies instead of the one, as previously requested by Scherer (Serial No. 056 dated October 15, 1998). Dr. Shellenberger replied that Scherer made this request because of concern over adequate powering of the two independent but identical studies, since enrollment was not occurring at the rate they anticipated. When Scherer transferred the rights to this IND to Elan, Elan decided to take a more conservative approach, and continued the enrollment to the numbers necessary for the two studies independently. The statistical analysis plan for the two studies was then subsequently submitted to the Agency for review and approval and amended following FDA comment (October 15, 1999) in a submission dated 10 December 1999 (Serial No. 078). These actions occurred prior to completion of the studies and breaking of the blind. b(4)

There was a discussion of the magnitude and nature of the placebo response in PD studies. \_\_\_\_\_ commented that larger placebo responses can occur in this kind of b(4)

trial. It was suggested that the literature review include Parkinson's Disease studies of therapies other than selegiline and that a discussion of the placebo response should be provided.

### ***Clinical Studies / Exposure Data***

The safety database was then discussed with an N of 430 newly treated patients, with presentation of the studies to be included for this as well as the respective exposure time for these patients. Study Z/SEL/97/027, the extension study to 025 and 026 continues to add to this database, although the 1 year exposure exceeds ICH guidance requirements at this time. In examining the adverse event profile, Dr. Shellenberger pointed out the most common adverse events and general similarity to the placebo groups. He pointed out the relatively higher incidence of "stomatitis" that may have occurred from an amalgamation of a variety of verbatim adverse events which may not be stomatitis (e.g. "discrete areas of focal reddening"). No serious adverse events were associated with this term nor did any of the patients withdraw from the study due to "stomatitis". Later, Dr. Shellenberger asked if the events could be broken down into the various sub-components to more accurately depict the actual events. Dr. Katz accepted this means for reporting them.

Dr. Katz asked if a tyramine challenge test was done comparing the Zydis formulation with Eldepryl. Dr. Shah presented the data from such a study, which included comparisons of Zydis selegiline at 1.25 and 10 mg doses to that of conventional selegiline tablets at 10 mg (single dose). Although the data suggested a linear relationship, Dr. Katz requested that Elan repeat the study in a similar design to demonstrate that the 2.5 mg dose would be similar to that found for the 10 mg (5 mg bid) standard dosage form. Elan agreed to provide steady-state data from a similar oral tyramine challenge study (PK/PD) with Zydis selegiline 2.5 mg compared to 5 mg bid commercial dosage form.

### ***Labeling***

Dr. Katz also mentioned that, if approved, the language in the labeling would reflect the data provided, i.e., there would be no advantage to the Zydis formulation over the conventional tablet form. Additionally, he stated that the Eldepryl package insert is an older style, and the Zydis selegiline package insert would likely be simpler in some of the sections.

### ***Summary and Conclusion***

Dr. Scaife ended the Elan presentation by providing a summary and conclusion. Dr. Katz asked that the statistical analysis plan be followed as previously agreed upon, and that the robustness of Study 026 be confirmed. Following the meeting, the FDA faxed details of the format by which the statistical reviewer wanted the data presented (see attached). The FDA was also interested in viewing the combined analysis of the two studies, which still provided a statistically significant positive result for the primary endpoint. Dr. Scaife confirmed with the FDA the acceptability for submission and subsequent filing by the FDA for review of a Section 505(b)(2) NDA for Zydis® selegiline using the one positive efficacy study (Z/SEL/97/026) in combination with the other supportive studies for safety and other required information supportive of this type of filing, based on the data presented in the meeting. Representatives of Elan thanked the FDA attendees for their time and consideration of the information presented.

### **Attachments:**

- Fax from Dr. Sharon Yan via Ms. Teresa Wheelous of 31 January 2001
- Paper copies of overheads presented at the meeting

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

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Russell Katz  
6/5/01 09:36:22 AM

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21 Page(s) Withheld

X Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

**END OF PHASE II TELECON  
IND 47,005**

**Drug:** Zydis Selegiline (Zelapar)  
**Sponsor:** Scherer DDS  
**Date:** January 11, 1999  
**Conversation Between:**

Agency:  
 K. Jin – Biometrics  
 L. Freed – Pharmacology  
 R. Tresley – Medical  
 S. Yan – Biometrics  
 I. Mahmood – Biopharm  
 R. Katz – Acting Director  
 G. Fitzgerald – Pharmacology  
 T. Wheelous – Project Manager

Sponsor:  
~~\_\_\_\_\_~~  
 J. Watson – Regulatory Affairs (Scherer DDS)  
~~\_\_\_\_\_~~  
 N. Mallard – Research Scientist  
 T. Clark – Operations Manager

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**Purpose:** Discuss outstanding requirements necessary for a 505(b)(2) NDA submission for Zydis Selegiline.

**Discussion:**

**I. Combining Data from two identical studies (#25 and #26) into one study to demonstrate efficacy in support of a 505(b)(2) NDA.**

It is acceptable to combine studies #25 and #26 with the following caveats:

- A 6-week interim analysis, previously proposed, will not be conducted.
- A formal statistical amendment will be submitted to include a new analysis plan for the combined study

**II. Confirmation that no additional pre-clinical and pK studies are required for the 505(b)(2) submission.**

**Pre-Clinical Work-up to support 2.5 mg Zydis Selegiline**

• From the sponsor's summary, it would appear that plasma levels of selegiline following the 2.5 mg dose of the Zydis formulation exceed the plasma levels obtained after a 10 mg daily dose of the marketed oral formulation. If so, additional preclinical data may be needed. The data are not entirely clear on this issue. The sponsor should provide a summary table comparing the plasma exposure obtained with the Zydis formulation at the intended clinical doses to those obtained with the marketed oral formulation at 10 mg/day. Both  $C_{max}$  and AUC should be included.

• A one-month study should be conducted in order to assess the potential for Zydis Selegiline to produce adverse effects on the oral mucosa. Both intact and abraded oral mucosa should be tested, and observations should include a

complete histopathological evaluation of the oral cavity. The choice of species to be used should be justified; the rat and hamster are usually acceptable species.

PK (Biopharmaceutical Concerns):

- The sponsor believes, based upon bioavailability data from over 100 patients on the approved selegiline formulation (Eldepryl), that the bioavailability of selegiline is extremely variable.
- Study #19008 shows pK values ranging from low to very high levels. The sponsor reports that the AUCs for the 1.25 mg and 2.5 mg formulations are within the approved product, Eldepryl, range and should be covered by the Eldepryl data.
- The distribution of AUCs for Zydys selegiline appears to be heavily shifted to the higher end and most of the AUCs for Eldepryl are at the lower end of the range. The sponsor should address the difference in the positioning of most of the AUCs for Zydys Selegiline relative to the positioning of most of the Eldepryl AUCs.
- The Cmaxs are within Eldepryl's range as well, but are more variable.
- Population pK will be provided in the NDA.
- Parent plasma levels as well as metabolite plasma levels should be studied.
- At the time of the Eldepryl approval the ability to test for selegiline blood levels was not available. Blood levels after first pass demonstrating levels of selegiline are needed to support the NDA.

**III. Acceptability of the size of the proposed safety database for a 505(b)(2) submission.**

- Ordinary NDA database requirements for Parkinson's Disease drugs are 300 patients for 6 months and 100 patients for 1 year.
- The sponsor has a database of 146 patients for 6 months and 77 patients for 1 year.
- The sponsor believes that an exception to the ordinarily required NDA database should be granted to this application because selegiline tablets have been marketed for many years and the safety profile is well defined.

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**ACTION ITEMS:**

1. The sponsor will submit a protocol containing a new proposal report and analysis plan for combining the two studies.

2. The sponsor should conduct an animal oral mucosa study of at least one-month duration to include histology of both the intact and abraded mucosa.
3. The sponsor will provide data supporting plasma levels of the parent and all metabolites to cover the higher strength Zydys selegiline formulation, 2.5 mg.
4. The sponsor will provide an argument supporting a smaller than usual safety database.

HFD-120

/Katz

/R. Tresley

/G. Fitzgerald

/L.Freed

/T. Wheelous

HFD-710/K. Jin/ S. Yan

HFD-860/Mahmood

Draft 1/22/99, 3/1/99, 3/11/99

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# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

## Volume 1

Application Information	
NDA 21-479	
Drug: Zelapar (zydis selegiline orally disintegrating) Tablets 1.25 mg	Applicant: Valeant (formerly Elan) Pharmaceuticals International
RPM: T. Wheelous	HFD- 120 <span style="float: right;">Phone # 301-796-1161</span>
Application Type: 505(b)(1) ( <input checked="" type="checkbox"/> ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): Eldepryl (selegiline) Tablets NDA 19-334
❖ Application Classifications:	
• Review priority	( <input checked="" type="checkbox"/> ) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	June 14, 2006
❖ Special programs (indicate all that apply)	( <input checked="" type="checkbox"/> ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( <input checked="" type="checkbox"/> ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes ( ) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
<b>A</b> Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	( ) Verified
<b>B</b> Patent	
• Information: Verify that patent information was submitted	( ) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(i)(A) ( ) I ( ) II ( ) III ( ) IV
21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)	21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
"Certifications for the listed drug. As provided in Section 1.2 and 1.3 (Item 1, Volume 1, Page15-16) of the original Zelapar™"	

<p>NA, 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)."</p>	
<p>Patent number(s): 5,648,093 exp: July 15, 2014 Drug Product (Composition)</p> <ul style="list-style-type: none"> <li>For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).</li> </ul>	( ) Verified
<p><b>C</b> Exclusivity Summary (approvals only)</p>	
<p><b>D</b> Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</p>	<p>5-23-06 9/7/05 – Appendix B</p>
<p><b>E</b> Actions</p>	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	(X) AP ( ) TA ( ) AE ( ) NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	AE – 2/7/03
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
<p><b>F</b> Public communications</p>	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>	( ) Yes (X) Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
<p><b>G</b> Labeling (package insert, patient package insert (if applicable), Med Guide (if applicable))</p>	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)</li> </ul>	<p>DMETS – 6/2/06 DMETS – 1/26/06 DDMAC – 9/1/05 DMETS -9/14/05 DMETS- 7/5/02</p>
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
<p><b>H</b> Labels (immediate container &amp; carton labels)</p>	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>Applicant proposed</li> </ul>	
<ul style="list-style-type: none"> <li>Reviews</li> </ul>	
<p>Post-marketing commitments</p>	
<ul style="list-style-type: none"> <li>Agency request for post-marketing commitments</li> </ul>	

<ul style="list-style-type: none"> <li>Documentation of discussions and/or agreements relating to post-marketing commitments</li> </ul>	
<b>J</b> Outgoing correspondence (i.e., letters, E-mails, faxes)	
<b>K</b> Memoranda and Telecons	
<b>L</b> Minutes of Meetings	
<ul style="list-style-type: none"> <li>EOP2 meeting (indicate date)</li> </ul>	1-11-99
<ul style="list-style-type: none"> <li>Pre-NDA meeting (indicate date)</li> </ul>	11-7-01 & 1-30-01
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (indicate date; approvals only)</li> </ul>	May 2006
<ul style="list-style-type: none"> <li>Other – End of Review Telecon (see Tab K)</li> </ul>	4-25-03
<b>M</b> Advisory Committee Meeting	
<b>N</b> Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
<b>O</b> Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	10/24/05 – Group Leader 2/7/03 – Div. Director 2/7/03- Team Leader
<b>P</b> Final review(s) <i>(indicate date for each review)</i>	6/13/06 1-10-03

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VOLUME 2

<b>Q</b> Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	12-10-02
<b>R</b> Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	1-10-03
<b>S</b> Pediatric Page(separate page for each indication addressing status of all age groups)	
<b>T</b> Statistical review(s) <i>(indicate date for each review)</i>	6-9-03 1/16/03
<b>U</b> Biopharmaceutical review(s) <i>(indicate date for each review)</i>	5/16/06 9/21/05, 9-15-05 5-20-02
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
<b>V</b> Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
<b>W</b> CMC review(s) <i>(indicate date for each review)</i>	6-8-04 5-29-03 2-4-03
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	12-10-02 1-13-03
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Pharm/Tox Information	
<b>XYZ</b> ❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	2-6-03 Reviewer & Team Leader
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	
❖ CAC/ECAC report	

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