

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-479

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-479

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

Dear Dr. Schary:

Please refer to your new drug application (NDA) dated March 29, 2002, received April 8, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zelapar (zydis selegiline orally disintegrating) 1.25 mg Tablets

We acknowledge receipt of your submissions dated:

31-Dec-2002	10-Jan-2003	15-Jan-2003	17-Jan-2003
31-Jan-2003	17-Feb-2003	04-Apr-2003	16-May-2003
07-Aug-2003	31-Oct-2003	07-Nov-2003	27-Feb-2004
16-Mar-2004	16-Mar-2004	30-Apr-2004	25-Jun-2004
15-Dec-2004	30-Dec-2004	10-Jan-2005	19-Jan-2005
26-Jan-2005	04-Feb-2005	16-Feb-2005	29-Mar-2005
31-Mar-2005	27-Apr-2005	04-May-2005	06-May-2005
12-May-2005	17-May-2005	27-May-2005	07-Jul-2005
19-Jul-2005	25-Jul-2005	03-Aug-2005	04-Aug-2005
04-Aug-2005	23-Aug-2005		

The March 29, 2005 submission constituted a complete response to our February 7, 2003 action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following concerns.

As you know, in our Approvable letter of February 7, 2003, we asked you to adequately characterize the metabolism of selegiline. Specifically, we asked you to identify the CYP450 enzymes responsible for selegiline metabolism, as well as to characterize the inhibition and induction potential of selegiline. We further noted that *in vivo* drug-drug interaction studies might be required, depending upon the results of the metabolic studies. We acknowledged that it might be possible to provide the requested data from literature articles, but that if the literature were inadequate, you would need to perform your own studies.

You have chosen to submit literature reports to respond to our requests. Unfortunately, these reports present, at best, an unclear, and, at worst, a conflicting, picture of selegiline's metabolism.

Specifically, the article by Taavistan, et al (**Selegiline Metabolism and Cytochrome P450 Enzymes: In Vitro Study in Human Liver Microsomes**. *Pharmacology and Toxicology* 2000. 86, 215-221) documents CYP1A2 and CYP3A4 as the important metabolizing enzymes. However, the article by Hidestrand et al (**CYP2B6 and CYP2C19 As the Major Enzymes Responsible for the Metabolism of Selegiline, a Drug Used in the Treatment of Parkinson's Disease, as Revealed From Experiments with Recombinant Enzymes**. *Drug Metabolism and Disposition* 29:1480-1484, 2001) suggests that CYP2B6 and CYP 2C19 are the major metabolic enzymes (apparently, the latter authors examined the contribution of 1A2 and 3A4, and found them not to be important, and the former authors examined the effects of 2C19, and found it to be unimportant).

However, other authors have found that genetic polymorphisms for CYP2C19 did not result in differing selegiline levels (Laine et al. **CYP2C19 polymorphism is not important for the in vivo metabolism of selegiline**. *European Journal of Pharmacology* (2001) 57: 137-142). Further, other authors have found that inhibition of CYP3A4 does not result in appreciably elevated plasma levels of selegiline (Kivisto et al. **Selegiline Pharmacokinetics are unaffected by the CYP3A4 inhibitor itraconazole**. *European Journal of Pharmacology* (2001) 57: 37-42.). These articles suggest that these two enzymes may not be important in the metabolism of selegiline. These findings are also compatible with multiple enzymes being responsible for selegiline metabolism, with none being predominant. However, the data are clearly not definitive.

Other articles provide additional relevant data that appear inconsistent with some the data described above.

Laine et al. (**Dose linearity of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids**. *British Journal of Clinical Pharmacology*(1999) 47:249-254) have documented 15-40 fold elevations in plasma selegiline levels in patients taking concomitant oral contraceptives (gestodene/ethinylestradiol or levonorgestrel/ethinylestradiol) compared to patients not taking contraceptives. Some of these sex steroids are considered significant inhibitors of CYP3A4. However, another group found no appreciable increase in plasma selegiline levels in patients receiving concomitant hormone replacement therapy (Palovaara et al. **Effect of concomitant hormone replacement therapy containing estradiol and levonorgestrel on the pharmacokinetics of selegiline**. *European Journal of Pharmacology* (2002) 58: 259-263.). We note that the hormone replacement therapy studied involved estradiol valerate and not conjugated estrogens; the latter is probably the most common hormone replacement therapy used in the U.S.

These findings taken together present an extremely confusing picture of selegiline metabolism. For this reason, we have concluded that you have not presented an adequate characterization of selegiline metabolism. As requested in the original Approvable letter, then, we ask that you do so. It appears to us that you will need to perform your own series of adequate *in vitro* (and perhaps *in vivo* tests) to adequately establish the pathways of selegiline metabolism.

In addition to the findings described above, we have reviewed another recent publication that bears on the question of selegiline metabolism and elimination. Although you have commented on this publication in response to our questions, we do not believe that your responses adequately address the concerns described below.

Anttila et al (**Marked effect of liver and kidney function on the pharmacokinetics of selegiline**. *Clinical Pharmacology and Therapeutics* 2005;77:54-62) describe significantly increased selegiline levels in patients with hepatic dysfunction or renal dysfunction. Specifically, these authors found plasma levels of selegiline increased in patients with hepatic disease to about 18 times those seen in normals, and in patients with renal disease to about 6 times those seen in normals. Significantly, the degree of either hepatic or renal disease in the patients studied did not seem particularly severe based upon mean serum aminotransferase and creatinine and BUN levels, and the authors state that there was no correlation between disease severity and selegiline levels. Interestingly, these authors also studied patients receiving treatment with anticonvulsant drugs (known to be inducers of hepatic metabolism) and selegiline, and noted levels of selegiline in these patients that were about 1/20th of those seen in normals.

Although this paper does not provide sufficient details to permit an independent analysis of the data, the results are disturbing. If true, they raise serious questions about our ability to draft product labeling that could ensure that only patients not at risk to achieve these elevated selegiline levels would receive the drug. This is true independent of our concerns, expressed above, about the propriety of approving Zelapar in the absence of detailed information about the metabolism of selegiline.

Specifically, as noted, the degree of hepatic or renal disease in the patients studied appeared relatively mild. Many patients with Parkinson's Disease who might be candidates for treatment with selegiline would be expected to have this degree of either hepatic and/or renal disease, raising the question of the safety of selegiline in these patients. Of course, we have no well-documented experience with the safety of the higher levels of selegiline that would result in these patients. We could presume, at the very least, that selegiline would lose its selectivity for MAO-B inhibition, and that dietary restrictions would need to be imposed. Of course, there may be additional safety concerns (for example, although we do not believe that you have identified a clear signal of QTc prolongation to date up to a 10 mg daily dose of Zelapar, the levels that could be achieved in patients with hepatic disease would be far in excess of those studied). Although we recognize that in our Approvable letter of February 7, 2003 we agreed that you could perform studies in patients with hepatic or renal disease in Phase 4, clearly the results of this recently published study raise important new questions about the safety of selegiline in these patients. For this reason, we believe it is important to resolve these questions before adequate labeling could be drafted. Therefore, we request that you further evaluate, prior to approval, the kinetics (and possibly safety) of selegiline in patients with hepatic or renal dysfunction. We strongly suggest that you consult with the Division prior to conducting any of the studies we have requested in this letter.

In addition, we believe that you have not addressed our request, included in the February 7, 2003 Approvable letter, to explain the discrepancy between the apparent opposite effects of food on the absorption of Zelapar and Eldepryl. We again request that you do so.

Finally, although we have concluded that you have demonstrated that selegiline is unlikely to inhibit CYP450 enzymes, you have not adequately documented its capacity (or lack thereof) to induce these enzymes. We again request that you do so.

LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the proposed labels and labeling for Zelapar, DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENT

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)**

B. BLISTER LABELS

1. Assure the established name is at least ½ the size of the proprietary name in accordance with 21 CFR 201.10(g) (2).
2. We encourage the inclusion of the finished dosage form "oral disintegrating tablets" in conjunction with the established name. For example: (Selegiline HCl) Oral Disintegrating Tablets.
3. Please revise the font or coloring scheme of the white lettering on purple background. As currently represented, the smaller font is difficult to read.
4. Consider an addition to the "Pull Here" statement, which would again warn patients not to attempt pushing the tablets through the foil.

C. POUCH LABELING (SACHET)

1. See Comments under A and B.
2. Provide a remark or guidance on how to open the sachet. This is to assure that the patient will not accidentally damage the internal contents.
3. Delete or reduce the prominence of the "Zydis" statement, as the introduction of this name may be confusing to the reader.
4. If the blisters should be stored in the sachet after opening, please add a statement to the labeling.
5. Increase the prominence of the product strength and relocate the strength to appear in conjunction with the proprietary and established names. The current presentation does not properly emphasize this critical information.
6. Referencing "Instructions for use", consider revising bullet #2 to read: ~~_____~~

~~_____~~ This provides a complete listing of how to take the medication for the patient on packaging that may be maintained. This could help to assure proper ingestion of Zelapar. **b(4)**

D. CARTON LABELING (sample and trade unit pouch)

See comments A and B and C-3 and 7.

Post Marketing Commitments

We acknowledge your agreement to conduct a complete battery of reproductive and developmental toxicology and genotoxicity studies in Phase 4.

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

Describe in detail any significant changes or findings in the safety profile.

When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.

Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

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

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology
5901-B Ammendale Road
Beltsville, MD 20705-1266

and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any question, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

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

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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Russell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-479

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

Dear Mr. Grilley:

Please refer to your new drug application (NDA) dated March 29, 2002, received April 8, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelapar (selegiline) 1.25 mg Zydis Tablet.

We acknowledge receipt of your submissions dated:

April 17, 2002	May 03, 2002	May 29, 2002
June 10, 2002	June 11, 2002	June 20, 2002
June 21, 2002	July 17, 2002	July 25, 2002
July 26, 2002	August 20, 2002	August 29, 2002
August 30, 2002	September 9, 2002	September 10, 2002
September 11, 2002	October 8, 2002	October 16, 2002
November 7, 2002	November 8, 2002	November 18, 2002
November 20, 2002	December 4, 2002	December 19, 2002
December 27, 2002	January 21, 2003	

We also acknowledge receipt of your submissions dated:

December 31, 2002	January 10, 2003	January 15, 2003
January 17, 2003	January 31, 2003	

These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following issues:

CLINICAL

We are concerned about the results you have obtained in your tyramine-challenge studies, in particular Study 101.

As you know, this study yielded a pressor ratio of 6.8 for Eldepryl, a value considerably greater than that previously obtained for this product. In addition, the percent of patients whose threshold dose of tyramine in the Eldepryl group was 50 mg or less was 59%, also a value at considerable variance with previous data for this product. The corresponding values obtained for your product displayed a

confusing pattern, with the Zydis 1.25 mg dose having the greatest response. If these values are accurate, they raise considerable concern about the potential for both your product and marketed selegiline products to produce considerable degrees of MAO-A inhibition and hypertensive crises in patients with unrestricted diets. However, there are a number of factors that make the interpretation of this study difficult, including the absence of both a placebo and a positive control group.

In addition, other data suggest that this study may have not evaluated the maximum potential MAO-A inhibitory effect of your product. Specifically, while some data suggest that steady state is reached in several days, other data suggest that accumulation may be occurring for up to four weeks. In particular, in Study 101, the AUC of selegiline at Day 10 was about 3-4 times that at Day 1, but in Study 96/014, the AUC at Day 28 was about 9-10 times that at Day 1. In addition, in Study 101, the C_{max} at Day 10 was about equal to that at Day 1, but in Study 96/014, the C_{max} at Day 28 was about 2-3 times that on Day 1. While we acknowledge that cross-study comparisons are problematic, these data do suggest that steady state levels of selegiline may not have been reached in Study 101.

Further, while we believe that food intake increases the absorption of Eldepryl by 2-3 fold, data in your application suggests that taking Eldepryl with food decreases the C_{max} by 2-3 fold. This disparity should be addressed, and may have consequences for the interpretation of your data.

For these reasons, then, we cannot agree at this time that a showing of similarity of response to tyramine challenge between your product and Eldepryl in Study 101 is comforting. Either both products produce considerable MAO-A inhibition (and would require dietary restrictions for safe use), the values for both are spurious, or the value for Eldepryl is spurious and the value for your product is not. Given the questions raised above, we cannot confidently choose which of these alternatives is true.

Therefore, while we request that you attempt to explain the results of this study, you will need to repeat a tyramine-challenge study in order to fully and adequately answer the question of whether or not your product, given as 2.5 mg once a day, produces appreciable inhibition of MAO-A. Such a study should incorporate features that address our concerns described above (status of food intake, duration, placebo and active control groups, etc.). We would strongly urge you to consult with us about the design of this study as soon as possible.

In addition to this, the following issues must be addressed before the application may be approved.

1. In study 25, LOCF analyses (of the same patient population), which appear to differ only slightly, result in a range of p-values from 0.1 to 0.8. This analysis-dependent outcome suggests some unusual pattern to the data. We ask you to investigate your analyses of study 25 and comment on these results.
2. Given the higher C_{max} expected with Zelapar 2.5 mg/day compared to the marketed selegiline formulation, we believe it is important to characterize changes in blood pressure in relation to dosing, ideally capturing results at T_{max}. Such data was not collected in the controlled trials, but was collected in study 101 (PK and tyramine challenge study). Unfortunately, the only analyses of the BP data from study 101 are based on mean changes; outlier analyses based on pre-defined clinically important changes would be more informative. We ask you to perform such analyses for both resting BP and orthostatic BP. Unfortunately, study 101 does not have a placebo-control group. Therefore, within the tyramine challenge study requested above, we ask that you include a

placebo-control group and again collect resting and orthostatic BP data in relation to timing of dose.

3. As with the blood pressure data above, we believe it is critical to investigate ECG data timed to dosing. This has not been done in any of your studies to date. ECG data (not timed to dosing) was provided initially for one controlled trial, study 25, and revealed a 7 msec prolongation of QT interval on Zelapar vs placebo. While not found in the other controlled trial, study 26, this still raises the possibility of QT prolongation with selegiline. Given the higher Cmax with Zelapar, we ask you to investigate the possibility of QT prolongation further. As with the BP data above, we believe ECG data in relation to dosing can be most efficiently collected within the new tyramine challenge study.

In addition to responding to the points listed above, it will be necessary for you to submit draft labeling revised as shown in the attachment to this letter. Note that there are numerous comments / questions embedded in the text, which you should address.

CMC

The following recommendations regarding the proper designation of the dosage form and container labeling were communicated to you in a July 15, 2002 facsimile:

Dosage Form Designation: You have labeled the drug product as an "Orally Dissolving Tablet." We request that "Orally Disintegrating Tablet", the USP accepted designation for this type of dosage form, be used.

Container Labels:

A. Blisters:

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. Pouch sample packaging:

1. See comment A2 and A3.
2. Increase the prominence of the established name.
3. Relocate the ~~statement to the side panel.~~ statement to the side panel.
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.

b(4)

C. 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~~ phrase on the sample unit carton packaging.

b(4)

In addition, we remind you of the commitments specified in your January 21, 2003 submission to develop a ~~_____~~ HPLC assay method for the drug product, and to establish a specification for ~~_____~~ in Zelapar Orally Disintegrating Tablets unless ~~_____~~ is demonstrated to be insignificant during manufacture of the tablets and on storage. This can be done post-approval.

b(4)

PRECLINICAL

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

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

Drug Metabolism

- a) In the labeling for Zydis selegiline, you have included a section on ~~_____~~ under 'DRUG INTERACTIONS'. This section lists ~~_____~~. Our literature search revealed that this was not a comprehensive list of isoenzymes responsible for the metabolism of selegiline. Various conflicting literature articles have been published regarding the metabolism of selegiline; however, you have referred to only one literature article. You should either conduct a thorough literature search and update the proposed label or conduct *in vitro* metabolism studies (if inadequate information is available in literature) to evaluate the CYP 450 isoenzymes responsible for the metabolism of selegiline and update the label based on the results of these studies.
- b) Also, characterize the inhibition/induction potential of selegiline by conducting *in vitro* studies or obtain this information from the literature if available.
- c) Additional drug-drug interaction studies may need to be considered depending on the information gathered on the metabolism of selegiline.

b(4)

Urinary Excretion

In volume 1, page 154, you state that the urinary excretion of selegiline and its metabolites is 86% of the oral dose with 59% being recovered as L-methamphetamine and 26% recovered as L-amphetamine. You also provide references associated with this sentence. We could not locate this information in the literature. Please highlight in the referenced article the section from which this information was obtained. It appears that only 44-58% of the dose has been recovered in the urine based on Shin's article.

Food Effect

It is unclear why the food effect observed in Study Z/SEL/96/008 is opposite to that known for the approved product Eldepryl. Please explain this discrepancy.

Gender Effect

Conduct a meta-analysis to characterize the effect of gender on the pharmacokinetics of Zydis selegiline and include appropriate information in the labeling of the product.

Phase 4 Commitments:

- a) Conduct a pharmacokinetic study in subjects with hepatic impairment.
- b) Conduct a pharmacokinetic study in subjects with renal impairment since selegiline is primarily excreted renally (although mostly as metabolites, these contribute to the activity of the drug to some extent).

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

*(please see electronic signature
on last page of document,
following attachment)*

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

Attachment: FDA Proposed Draft Labeling Text

16 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Russell Katz
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