

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-479

MEDICAL REVIEW

MEMORANDUM

DATE: June 13, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-479

SUBJECT: Action Memo for NDA 21-479, for the use of Zelapar (selegiline orally disintegrating tablets) in patients with Parkinson's Disease (PD)

NDA 21-479, for the use of Zelapar (selegiline orally disintegrating tablets; ODT) in patients with Parkinson's Disease (PD), was submitted by Elan Pharmaceuticals, Inc., on 3/29/02. This application has been the subject of two Approvable letters (2/7/03 and 9/30/05). Several issues were identified in the 9/30/05 Approvable letter that needed to be addressed by the sponsor (which had become VALEANT Pharmaceuticals International):

- 1) The sponsor had not performed adequate studies to identify the CYP450 enzymes responsible for the metabolism of selegiline. We had given the sponsor the option to present literature references that established the enzymes responsible for selegiline metabolism, if available. The literature submitted gave an inconsistent, essentially contradictory picture of selegiline's metabolism; therefore, in the Approvable letter, we asked the sponsor to perform adequate studies to answer this question.
- 2) A recent publication identified very large increases in selegiline plasma levels in some patients with impaired hepatic and renal function who received the marketed oral selegiline product. From the article, it appeared that there was no correlation between measures of hepatic/renal function and selegiline levels. The marked elevation of these plasma levels seen in this study raised significant concerns about the safety of selegiline in patients with what appeared to be relatively mild hepatic or renal disease. For this reason, we asked the sponsor to clarify this issue.
- 3) There was an apparent discrepancy between the effect of food on the kinetics of the ODT and the available oral selegiline; we asked the sponsor to address this discrepancy.
- 4) We asked the sponsor to address the capacity (or lack thereof) of selegiline to induce CYP450 enzymes.
- 5) We asked the sponsor to make changes to their proposed Blister Pack labels, Pouch labeling, and Carton labeling.
- 6) We had asked the sponsor to complete additional reproductive and developmental toxicology and genotoxicity studies in Phase 4.

The sponsor responded to the 9/30/05 letter in a submission dated 12/13/05. This submission has been reviewed by Dr. Leonard Kapcala, medical officer, Dr.

Vaneeta Tandon, Office of Clinical Pharmacology, Dr. David Claffey, chemist, Dr. Jinhee L. Jahng and Linda M. Wisniewski, Division of Medication Errors and Technical Support (DMETS), Dr. Denise Toyer, Alina R. Mahmud, and Carol Holquist, DMETS, and Dr. John Feeney, neurology drugs team leader. The clinical team recommends that the application be approved.

I will very briefly review the sponsor's responses to the issues raised in the 9/30/05 Approvable letter, and offer the rationale for the division's action.

1) Enzymes responsible for selegiline metabolism

As noted by the clinical team, the sponsor has performed adequate in vitro testing, and has identified 2B6 as the main CYP enzyme responsible for selegiline metabolism. CYP 3A4 has also been identified to play a role, but less so than 2B6. A study in which selegiline was given concomitantly with erythromycin (a 3A4 inhibitor) showed no increase in selegiline levels; this further supported the relatively minor role of CYP 3A4 in selegiline's metabolism. CYP 2A6 is also involved, but plays an even more minor role. Dr. Tandon describes in detail the reasons why the conflicting data in the literature are problematic, and why the sponsor's own in vitro data provide a more reliable picture of the enzymes responsible for selegiline's metabolism.

She also notes that there is reliable evidence that selegiline does not inhibit CYP450 enzymes, but that we still do not have adequate data on selegiline's potential to induce enzymes (although the sponsor did submit data intended to address this question, Dr. Tandon has concluded that it was inadequate), and she recommends that this issue be addressed in Phase 4.

2) Effect of hepatic/renal impairment on selegiline plasma levels

As noted above, an article in the literature suggested that in some patients with renal or hepatic impairment, very large increases in selegiline plasma levels were seen. As the various reviewers note, despite claims by the sponsor, there is no correlation between measures of organ impairment and plasma selegiline levels, and therefore the study is difficult to interpret. Dr. Tandon also points out several aspects of the study that suggest that the levels reported may be inaccurate (for example, the primary kinetic measure used in the article is the AUC, but the authors acknowledge that the half-life of selegiline, an accurate assessment of which is critical to this calculation, could not be estimated reliably).

An important point made by the sponsor is that the levels of selegiline in patients with hepatic impairment following the recommended dose of selegiline ODT will be considerably lower than those seen after the 20 mg of oral selegiline used by the authors of this study. Estimates of the levels seen after a 2.5 mg dose of ODT in patients with liver impairment approach those expected to be achieved after a 10 mg dose of ODT. As described by Dr. Kapcala, these levels appear to

be relatively well tolerated (they were examined in several studies, including a thorough QT study). Also, as described by Dr. Tandon, renal impairment would be predicted to result in an increase in plasma levels of selegiline metabolites.

Given the relative safety of plasma levels expected to be seen in patients with hepatic impairment, and the unreliability of the results described in the paper noted above, Dr. Tandon recommends that studies in patients with hepatic or renal disease should be performed in Phase 4.

3) Apparent discrepancies in food effect of ODT and oral selegiline

As noted in the 9/30/05 Approvable letter, a study by the sponsor suggested that selegiline plasma levels decrease when the ODT is given with food, but other data suggested that selegiline levels increase when the oral product is given with food. The sponsor has provided an argument as to why the effects seen with the oral selegiline were as documented (including factors related to BID dosing in that study and the ingestion of a lunch by patients in that study). Although their explanation is theoretical and cannot be considered especially compelling, the fact remains that they have performed their own adequate study, which documents a decrease in bioavailability of selegiline when given in the ODT formulation.

4) Does selegiline induce CYP450 enzymes?

The sponsor has not provided adequate data on the potential of selegiline to induce metabolic enzymes, and we will ask them to do so in Phase 4.

5) Changes to the Blister Pack labels, the Pouch labels, and the Carton labels

As noted above, we had asked the sponsor, in our 9/30/05 Approvable letter, to make several changes to the labels of the various portions of the packaging. Unfortunately, the sponsor had already produced a considerable amount of the packaging with the labeling to which we had raised objections in that letter. As a result, the sponsor has proposed that we permit the use of this packaging (so-called Campaign 1) until the supply is exhausted, at which point they propose that new packaging incorporating our requested changes (so-called Campaign 2, and which they have submitted for our review) be introduced.

I have discussed this proposal at great length with the review team, and I believe we have reached a consensus on this proposal. Specifically, although we agree that the packaging in Campaign 1 is not ideal, its use violates no regulation or policy, and, in my view, poses absolutely no additional potential for patient harm. For this reason, I believe it is reasonable to permit the sponsor to use this packaging; we have agreed with the sponsor (in a phone conversation of 6/13/06) that they will abandon the use of this packaging no later than 6 months

after approval. Further, in that conversation, the sponsor agreed to make several small changes to Campaign 2 packaging prior to its use.

I acknowledge that the DMETS reviewers have recommended that Campaign 1 packaging not be used, but, for the reasons stated above, I believe they can be approved.

In addition, Dr. Jahng of DMETS concluded that, when scripted, Zelapar and _____, appear very similar, and should not be permitted to co-exist in the marketplace. Senior staff in DMETS disagrees.

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I agree with the senior staff of DMETS. Given the fact that _____ and is not likely to be dispensed without a dosage strength (there is only one strength of Zelapar and it does not overlap with any strengths of _____ and is highly unlikely to be prescribed for once a day use (the only regimen to be approved for Zelapar), I believe that the existence of both names in the marketplace is not likely to result in medication errors (the question is apparently moot for the approval of Zelapar, given that _____ is not yet approved, as far as I know).

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6) Commitments for Phase 4 nonclinical studies.

The sponsor has agreed to perform the requested nonclinical studies by agreed-upon dates.

COMMENTS

The sponsor has responded adequately to most of the questions raised in our 9/30/05 Approvable letter. They have not yet adequately addressed the induction potential of selegiline, although they did attempt to do so. They have not definitively addressed the question of the effects of hepatic or renal impairment on selegiline plasma levels, although there are good reasons to presume that these levels will not be unacceptably excessive, and the predicted levels are expected to be well tolerated. For these reasons, these issues can be addressed in Phase 4, and we have received the sponsor's commitment to do so.

Also as noted earlier, the sponsor has not completely addressed our concerns about what we are now calling Campaign 1 packaging, but we believe that this packaging, though not ideal, poses no threat of patient harm, and can be used for a limited time. Again, we have obtained the sponsor's commitment to use this packaging for no more than 6 months after approval, and we have also obtained their agreement to make minor changes to the Campaign 2 labeling before its use.

The sponsor has agreed to complete the previously requested non-clinical studies in Phase 4.

Finally, we have agreed with the sponsor on product labeling.

For these reasons, then, I will issue the attached Approval letter, with appended agreed upon labeling.

Russell Katz, M.D.

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/s/

Russell Katz
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MEDICAL OFFICER

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**CLINICAL REVIEW OF RESPONSE TO APPROVABLE
LETTER**

Application Type 21479
Submission Number N000
Submission Code AZ

Letter Date 12/16/05
Stamp Date 12/16/05
PDUFA Goal Date 6/14/06

Reviewer Name Leonard P. Kapcala, M.D.
Review Completion Date 6/2/06

Established Name Zydis selegiline
(Proposed) Trade Name Zelapar
Therapeutic Class Monoamine oxidase B inhibitor
Applicant Valeant Pharmaceuticals

Priority Designation S

Formulation Zydis (oral disintegrating tablet)
Dosing Regimen Once daily
Indication Adjunctive treatment of patients
with Parkinson's disease who are
being treated with
levodopa/carbidopa and who
exhibit deterioration in the quality
of their response to this therapy

Intended Population Advanced Parkinson's Disease

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was not studied after multidosing under steady state conditions. Dr. Tandon's review (see her Comments shown above) notes these concerns/limitations. Furthermore, the sponsor's PK results in the original submission for study AN17933-101 showed that there were different ratios of selegiline AUC for 2 higher doses of Zydys selegiline (i.e. successive two fold dose increments; 2.5 mg, and 5 mg daily vs 1.25 mg daily) for data at day 1 vs day 10 (at PK steady state).

The sponsor's response and Clinical Pharmacology review both suggest that the increased plasma selegiline observed in another publication in which subjects were given increasing single doses (5, 10, 20, 40 mg) after treatment with an oral contraceptive regimen 75 µg gestodene/ ethinyl estradiol 30 µg was most likely related to gestodene and its inhibitory effects on the CYP 3A4 pathway. Although Dr. Tandon notes that gestodene could inhibit the CYP 1A2 pathway, this pathway is not believed to play any significant role in selegiline metabolism. Thus, these results seem contradictory of the results of the in vivo study with itraconazole.

Furthermore, when labeling ordinarily describes that the CYP 3A4 pathway is thought to be involved as major metabolic pathway in a drug, significant attention is given to the fact that inducers **and** inhibitors of this pathway should be avoided or at least used with caution. The Clinical Pharmacology label review recommends caution for concomitant use of CYP 3A4 inducers but does not recommend any similar caution about the concomitant use of inhibitory drugs for this pathway. Consequently, I cannot understand how this is a consistent approach. In summary, I think that there seems to be a "mixed," conflicting message about the potential importance or relevance of the CYP 3A4 pathway by noting that the CYP 3A4 enzyme is part of a major metabolic pathway for selegiline and that inducers of this pathway should be used with caution, but that there is no concern nor caution for the concomitant use of inhibitors of this pathway. **I think that the best way to resolve this issue would be to conduct a phase 4 in vivo study assessing the effect of an appropriate dose of a CYP 3A4 inhibitor at steady state on the steady state plasma levels of selegiline and its metabolites.**

Until this seeming confusion is resolved, I think that it would be appropriate, at the least, to note in the label that inhibitory drugs (e.g. ketoconazole, diclofenac, clarithromycin, etc.) should be used with caution, as the sponsor has proposed.

Clinical Reviewer Conclusions

- I concur with the Clinical Pharmacology reviewer's conclusions about the CYP 450 enzymes (CYP 2B6 and CYP 3A4 = major pathways; CYP 2A6 = minor pathway) involved with the metabolism of selegiline.
- I think that the label should note(at the least) caution about the concomitant use of CYP 3A4 inhibitors and that the best way to resolve conflicting data about the importance and relevance of the CYP 3A4 pathway to selegiline metabolism is by conducting a more appropriate, definitive drug-drug interaction study.

appropriate to conduct a phase 4 study to assess the drug-drug interaction potential of “high dose” conjugated estrogens and medroxyprogesterone acetate (e.g. perhaps 0.625 mg Premarin and 10 mg medroxyprogesterone acetate) on plasma levels of selegiline and its metabolites. However, I have been informed by my Clinical Pharmacology colleagues that the abundance of CYP 3A4 enzymes is so great that my concern is not a realistic one and that one would not expect increased selegiline exposure from concomitant use of conjugated estrogens and medroxyprogesterone acetate.

Clinical Reviewer Conclusion

- **I concur with the Clinical Pharmacology review that additional drug-drug interaction studies assessing effects of any oral contraceptive regimen or any HRT regimen on plasma selegiline exposure and its metabolites are not warranted.**

Potential of Selegiline as an Inhibitor for CYP 450 Enzymes

Clinical Reviewer Conclusion

- I concur with the Clinical Pharmacology reviewer’s conclusion that selegiline does not appear to inhibit CYP 450 enzymes.

Potential of Selegiline as an Inducer for CYP 450 Enzymes

Clinical Reviewer Conclusion

- I concur with the Clinical Pharmacology reviewer’s conclusion that the induction potential of selegiline has not been adequately characterized and that an *in vitro* study should be requested as a Phase 4 commitment.

Need to Determine the Separate Effect of Renal and Hepatic Functional Impairment on Plasma Selegiline Levels (i.e. Exposure)

Clinical Reviewer Comments

- The publication noted that there did not appear to be any correlation between severity of hepatic or renal impairment and elevation of plasma selegiline exposure. I fully concur with this assessment based upon all the information that I have seen.

A significant limitation in the patients with liver dysfunction in this publication is that there was no classification according to the Child-Pugh categories as “mild,” “moderate,” or “severe” hepatic impairment. This classification is typically applied to cirrhotic patients to assess the level of surgical risk and is also often used for classifying patients to be studied in clinical pharmacology studies investigating the effect of various degrees of

hepatic "impairment" on drug exposure. When considering hepatic functional impairment, it is critical to recall that elevated serum aminotransferase levels (e.g. serum ALT and/or AST) are poor indices of functional impairment but are considered better indices of liver injury than liver "function." Although a variety of tests can be used to assess or reflect the level of hepatic "function," more routine/standard laboratory tests that are considered to reflect impaired hepatic "function" better include increased serum bilirubin, prolonged/increased prothrombin time, and decreased serum albumin. The degree of abnormal alteration of these parameters can further reflect the severity of hepatic "impairment."

When one looks at the serum bilirubin and serum albumin of subjects studied (see Clinical Pharmacology reviewer, Dr. Tandon's review, Table 2, page 32), there is no good correlation between abnormalities of these parameters and plasma selegiline exposure. Serum albumin is within the normal range for all 10 subjects and the serum bilirubin was increased only in 4 subjects (2 of whom showed borderline elevation of 20 $\mu\text{mol/L}$ with normal being < 20). Of the 4 subjects with increased plasma selegiline exposure, only one showed a clear elevation (61) of serum bilirubin and another showed a borderline elevation of 20.

NOT FOR PUBLIC DISCLOSURE (bold text immediately below)

There was no information known about prothrombin time nor whether any subjects had ascites or encephalopathy (other parameters used for Child Pugh classification. Despite the fact that this information was specifically included in the publication, I had contacted the first author of the publication (Markku Anttila) and made specific inquiries about this information but he was only able to provide information on serum albumin and bilirubin. In addition, I had asked (via e-mail) Markku Anttila to call me or give me a phone number to call me to try to discuss this study and possible reasons for the puzzling findings but he has not given me his phone number nor called me.

END OF NOT FOR PUBLIC DISCLOSURE

- I disagree with the sponsor's conclusive response shown below (in italics) here that indicates that increased plasma selegiline levels occur only in "those patients which had severe liver impairment."

"After contacting one of the co-authors of the Anttila et al (2005) study, _____ was informed that the 4 hepatic patients with the significantly elevated selegiline plasma levels relative to the normal control subjects had biopsy confirmed cirrhosis and marked impairment in liver function. This indicates that the increased selegiline plasma levels reported by Anttila et al (2005) were obtained only in those patients which had severe liver impairment, whereas the remaining 6 hepatic patients with a lesser degree of liver impairment had almost the same selegiline plasma levels than normal patients."

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I asked the sponsor specifically to provide information regarding who (sponsor's consultant) had contacted and what specifically was communicated. The sponsor provided copies of the "string" of e-mails between _____ and the third co-author (Dr. Olavi Pelkonen). My review of all of this e-mail correspondence does not find information/data supportive of the sponsor's contention disputed above here. Of interest, some pertinent comments by Dr. Pelkonen note that "We did not perform Child-Pugh classification, but clinical markers can be found in the paper and they clearly show that the liver disease group differed from the others. On the other hand, I'd think that there was no really extremely severe liver condition in the group." Furthermore, _____ noted 2 assumptions : 1) "that the 4 subjects with the very high blood levels had histologically confirmed cirrhosis;" and 2) that the statement in the publication that increased selegiline levels was not correlated with severity of liver disease "was an attempt to correlate with liver chemistries and not histology." To this, Dr. Pelkonen responded : "this is true; all of them had histologically confirmed cirrhosis. Only one of those with histologically confirmed cirrhosis had pretty low selegiline max concentration."

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I emphasize the fact that a subject had cirrhosis does not necessarily equate with the view that the subject also had significant hepatic impairment of hepatic "function." It is also clearly known that subjects can have significant impairment of hepatic "function" in the absence of cirrhosis and that it is not always easy to know the level of hepatic "function." I also emphasize that one of the 5 subjects with biopsy proven cirrhosis did not have any elevation of selegiline exposure.

Altogether considering all available information, it is not possible to explain precisely why the 4 subjects with elevated plasma selegiline exposure had this increased exposure and why the other 6 subjects did not. Thus, it is not clear whether : 1) the 4 subjects with elevated selegiline exposure had that abnormality because of moderately or severely impaired hepatic "function" that was not clearly ascertainable; or 2) whether there was some other reason for the elevated exposure. Ordinarily, if the level of impairment of hepatic function was responsible for increased selegiline exposure, one would expect to be able to correlate selegiline exposure with the severity of hepatic functional impairment. Because I cannot do this, I am not certain that one can necessarily argue as the sponsor seems to do, that one should be cautious about using selegiline ONLY in subjects with "severe" hepatic disease, particularly when the sponsor does not define what is considered "severe" hepatic disease.

- The sponsor has provided a report by a consultant _____ that assesses "The prevalence of undetected renal and hepatic impairment." The report appears to be a reasonable attempt to assess the prevalence of renal and hepatic undetected (i.e. "unknown"/unrecognized) impairment and particularly the frequency of levels of severity of each impairment. **I think that it is important to note that that the report has an underlying theme that both hepatic and renal impairment can not only be asymptomatic but also "unknown" or unrecognized by a significant percentage/proportion of subjects and their physicians. It also seems clear that not**

b(4)

- The results of the publication by Anttila et al are clearly puzzling and do not seem to make sense in terms of the inability to correlate increased selegiline exposure directly with the apparent level of renal or hepatic impairment. Nevertheless, I do not think that these results can be dismissed but rather consider them to be of potentially significant clinical safety import, and merit attention. Regardless, I think that it is possible to draft labeling that would be reasonably informative. I think that the following elements should be contained in the label;

1) [REDACTED]

2) [REDACTED]

3) [REDACTED]

4) [REDACTED]

b(5)

- Of potential relevance to this application, the sponsor responded to my specific inquiry and informed me that the renal impairment PK study was nearly completed (only 5 of 6 subjects in the "severe" need to complete the study; other study groups including mild and moderate impairment dialysis patients and healthy matched subjects have completed the study). In contrast, the hepatic impairment PK study remains far from completed and has only completed dosing in all subjects with moderate hepatic impairment and in only 1 of 6 subjects (planned) with mild hepatic impairment. The sponsor has also noted that the site at which the study was being conducted will no longer be participating and that it may be some time before this study is completed. Although it may be some time, perhaps at least a year before the results of the sponsor's ongoing renal and hepatic impairment studies are available for updating the label, I think that adequate language can be drafted pending availability of these results.
- Finally, I will comment on some comments (shown in italics and quoted below) of the Clinical Pharmacology reviewer, Dr. Tandon, requesting evaluation by the Medical Officer.

"This reviewer recommends the studies be conducted as a Phase 4 commitment.

The potential accumulation following oral buccally absorbed Zelapar™ will be much lower (estimated to be 3-5 fold by the sponsor, given the difference in metabolic ratios).

However, the overall safety from higher exposures at steady state (5-6 fold higher) with suprathapeutic doses of 10 mg Zelapar (from tyramine challenge study, QTc study) should be evaluated by the Medical Officer."

I agree that it seems reasonable to conduct/complete the renal and hepatic impairment studies with Zydys selegiline as a phase 4 commitment. The following major reasons support this view :

- 1) increased exposure from Zydys selegiline (and its metabolites) via buccal absorption associated with renal or hepatic functional impairment would be expected to be considerably less than exposures from swallowed selegiline (i.e. Eldepryl);
- 2) the publication raising concerns about renal and hepatic impairment contains puzzling results that do not clearly seem scientifically sound mainly because of the inability to correlate increased exposure directly with increased impairment;
- 3) the reproducibility of the results of the publication seems unlikely likely;
- 4) the safety experience observed in short term PK studies of a high dose (10 mg/d) of Zydys selegiline in healthy volunteers and a longer term controlled study (# 8) of patients with Parkinson's Disease did not exhibit a substantially, or markedly different safety profile for Zydys selegiline than exposure to lower doses (e.g. ≤ 2.5 mg daily);
- 5) the label can be adequately crafted to deal with the potential safety implications of increased selegiline exposure associated with renal or hepatic functional impairment.

I would particularly also like to note that the most recently conducted tyramine sensitivity study did not suggest a significant risk for hypertensive responses with significant oral tyramine exposure when Zydys selegiline exposure is increased up to 4 fold over the recommended daily dose (2.5 mg/d). Neither did the "thorough" QTc study suggest a clear indication of QTc prolongation with a similarly increased exposure (e.g. 4 fold increase with 10 mg/d). Nevertheless, this study was not able to exclude a possible 10 msec increase in QTc prolongation with the 10 mg daily dose when confidence intervals were analyzed. Thus, if patients were to be exposed to very high selegiline exposures (e.g. greater the 4 fold increased exposures expected with 10 mg daily), it is difficult to comment on the nature and severity of safety issues that might arise or be experienced.

2 INTRODUCTION AND BACKGROUND

2.1 Background on Conventional Selegiline (Eldepryl®)

Conventional selegiline is currently approved (1989) in the U.S. as well as in several other countries for the treatment of patients with Parkinson's disease (PD) who are receiving levodopa/L-DOPA (LD) therapy (with or without a peripheral decarboxylase inhibitor) and who are experiencing deterioration in their therapeutic response to LD. Selegiline is thought to exert its therapeutic effect via inhibition of the monoamine oxidase (MAO) B enzyme and the decrease in dopamine metabolism and turnover. Selegiline is marketed in the U.S. as Eldepryl®, a formulation that is swallowed. Throughout this NDA conventional selegiline may also be referred to as Eldepryl. Although Eldepryl has also been studied to determine if it exerts a neuroprotective effect on dopaminergic neurons of Parkinson's disease patients, convincing evidence has not yet been generated.

ELDEPRYL (selegiline hydrochloride) is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as 1-deprenyl.

The chemical name is: (R)-(-)- N,,2 -dimethyl- N-2 -propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol, and has a molecular weight of 223.75. The structural formula is as follows:

One very important safety concern with Eldepryl is the potential to produce hypertensive "cheese" reactions when tyramine-containing products are ingested and Eldepryl has exerted non-selective inhibition of MAO-A. Thus, the main warning in the Eldepryl label is against the use of higher than recommended doses (i.e. 5 mg BID). Severe syndromes with potentially a fatal outcome may also occur from a drug-drug interaction with various drugs such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and meperidine. Severe CNS toxicity associated with hyperpyrexia and death has been reported with the use of TCAs and conventional selegiline. Severe reactions consisting of diaphoresis, flushing, ataxia, tremor, hyperthermia, hypertension/hypotension, seizures, palpitation, dizziness, and/or mental changes (e.g. agitation, confusion, and hallucinations potentially progressing to delirium and coma) have

been reported with the use of SSRIs and conventional selegiline. The occurrence of stupor muscular rigidity, severe agitation, and hyperthermia has been reported in some patients receiving the combination of meperidine and selegiline. Other main side effects from selegiline consist mainly of exacerbation of side effects produced by LD (e.g. nausea, vomiting, orthostatic hypotension, light headedness, syncope, hallucinations, dyskinesia, headache).

2.2 Pharmacology/Mechanism of Action of Selegiline

Selegiline (phenylisopropyl-N-methylpropylamine hydrochloride) belongs to the class of enzyme-activated irreversible inhibitors, also referred to as "suicide" substrates for monoamine oxidases (MAOs). MAOs are enzymes associated primarily with the outer mitochondrial membrane. MAOs are widely distributed throughout the body and are found in brain and in peripheral tissues such as the gut and heart. MAO catalyzes the deamination of monoamine neurotransmitters or neuromodulators among other substrates and occurs in two main forms, termed MAO-A and MAO-B. In humans, peripheral MAO is predominantly type A, while in the brain MAO is present as both forms; cortical MAO is predominantly type A, while in the striatum the predominant form is type B.

As a substrate selective for MAO-B, selegiline (L-selegiline isomer) acts in a two-step sequence, first binding to the enzyme active site then forming a covalent bond with the flavin moiety after deamination. After creation of the selegiline-enzyme combination, the MAO-B enzyme is permanently inactivated. The net result is a reduction in the ability of MAO-B to oxidize (degrade) amine neurotransmitters and neuromodulators. Restoration of MAO-B function can only be achieved through turnover of the inactivated enzyme and its replacement by synthesis of new enzyme, a process in humans that can take from two weeks up to 30-40 days to complete. When compared to other MAO-B inhibitors such as pargyline or moclobemide, and when given in therapeutically-relevant doses, selegiline displays a relatively high degree of selectivity for MAO-B. As a result, selegiline is expected to show improved tolerability and reduced potential for drug interactions than other, less selective MAO inhibitors.

Selegiline selectively and irreversibly inhibits monoamine oxidase Type B (MAO-B) and is used in Parkinson's disease patients to decrease the metabolism of dopamine and thereby enhance the effects of levodopa/L-DOPA (LD) and extend its effectiveness. In recent years, a number of other pharmacologic actions have also been identified for selegiline, including modulation of gene expression, modulation of apoptosis, and neuroprotective effects. The relationship of these potential actions of selegiline to its effectiveness in extending the action of LD in patients with Parkinson's disease is unclear.

2.3 Rationale for Zydys Selegiline Use

As LD has a relatively short half-life, requiring multiple doses during the day, the therapeutic approach to managing ON-OFF fluctuations is to pharmacologically extend the duration of each dose of LD by reducing the metabolism of the end product (dopamine) and its removal from the synapse via inhibition of MAO-B activity. This prolongation of dopamine's synaptic residence time essentially "smooths out" the rise and fall of dopaminergic stimulation delivered to the basal ganglia and is thought to reduce the stimulus driving the development of fluctuations in LD response.

A new formulation of selegiline (i.e. Zydys selegiline - ZS) was developed as an oral disintegrating tablet (ODT) for patients who might have swallowing difficulties related to advanced Parkinson's Disease and who might receive therapeutic benefit from a formulation that can be substantially absorbed via the buccal mucosa. Such a formulation would more efficiently deliver selegiline to the systemic circulation and would also avoid hepatic first pass effects that results in more extensive hepatic metabolism. Consequently, treatment with ZS is associated with lower levels of hepatic metabolites (i.e. amphetamine, meth-amphetamine, desmethyl-selegiline) and a lower risk of adverse reactions that may be related to metabolites.

2.4 ZS Approvals Outside U.S.

ZS has been approved outside the U.S. ZS was first approved in 1998 in the United Kingdom, was subsequently approved in 9 other countries, and approval is pending in another country (as of last information provided by sponsor). Approval is for adjunctive therapy of Parkinson's disease with LD and for symptomatic relief or to delay the need for LD in early Parkinson's disease.

2.5 Regulatory History

The original IND (47005) for ZS was submitted to the FDA in 1994 by RP Scherer DDS. When the sponsor discovered and notified FDA that ZS was not bioequivalent to conventional selegiline, it was clear that clinical efficacy data would be required to support the registration of ZS. In 1996 the DNDP informed Scherer that an open-label, randomized, controlled study (Z/SEL/95/008) of parallel groups of low and high ZS and Eldepryl would not be sufficient to support efficacy. Elan Pharmaceuticals took over the clinical development of ZS from Scherer in 1997. DNDP had recommended that the sponsor conduct a single, pivotal, "large" double-blinded, placebo-controlled study of ZS in Parkinson's disease patients but the sponsor planned to conduct two smaller studies (double-blinded, placebo-controlled, parallel group) with identical designs. In February 1999, Elan Pharmaceuticals assumed ownership of ZS from Scherer and completed pivotal studies Z/SEL/97/025, and Z/SEL/97/026, and their extension phase (Z/SEL/97/027). On 11/7/01 Elan Pharmaceuticals had a pre-NDA meeting with DNDP to

review mainly issues of format and content. Elan Pharmaceuticals and in addition to other Pre-NDA meetings previously for ZS: At the 11/01 meeting DNDP agreed that one positive, statistically robust study (e.g. study Z/SEL/97/026) could serve as the main basis for approval of ZS.

On 4/8/02, the sponsor (Elan) submitted this NDA for adjunctive treatment of Parkinson's Disease. On 2/7/03, an approvable letter was issued to the sponsor noting 2 main clinical concerns (conduct a tyramine sensitivity study and conduct a QTc study) among several other concerns of other disciplines. During the interim, Elan subsequently sold this product to another sponsor (Valeant Pharmaceuticals. There have also been interactions between the division and sponsor to provide advice to the sponsor. Most notably, there was a face to face meeting (5/25/04) with Valeant and the DNDP to discuss the study design for the tyramine sensitivity study and the QTc study. The sponsor did not follow much of the advice of the DNDP and markedly altered its study design for the tyramine sensitivity study. The DNDP had a teleconference with the sponsor to provide additional advice on the tyramine sensitivity study but the sponsor did not inform the DNDP that the tyramine sensitivity study had already been completed. The sponsor submitted (received 12/16/04) a response to the approvable letter by the new sponsor but this application was not filed because of deficiencies (significant deficiencies and problems related to the navigability of the application, no requested re-analysis of oropharyngeal adverse events, and other more minor ones). The sponsor's response was re-submitted and received by the Agency on 3/20/05.

A second approval letter was issued on 9/30/05. The DNP's main concerns revolved around pharmacokinetic (PK) issues that ultimately could impact on safety considerations. In summary, these PK issues related to the three areas : 1) questions about the metabolism of selegiline and the CYP 450 enzymes involved in its metabolism, selegiline's potential to induce and/or inhibit the CYP 450 enzymes, and the potential for oral contraceptives or hormone replacement therapy to interact with selegiline and increase selegiline exposure; 2) questions about effects of hepatic and renal impairment separately increasing selegiline exposure considerably; and 3) explaining/addressing the discrepant results of the food effect on ZS which was opposite to the food effect described in the U.S. label for swallowed selegiline (i.e. Eldepryl). This letter also asked the sponsor (in Comment # 4) to address some labeling issues (**related to the Chemistry discipline and which need not be addressed in this review**) and to provide a Safety Update.

On 11/8/05, the sponsor met with the DNP to review the concerns/issues identified in the second approvable letter. On 12/16/05, the sponsor submitted a Complete Response to the Approvable letter. This Complete Response is the subject of this review.

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2.6 Abstracted Executive Summary from Reviewer's Last Review (9/29/05 completion date) Including Conclusions and Recommendations

EXECUTIVE SUMMARY

Background and Introduction

Conventional selegiline is currently approved (1989) in the U.S. as well as in several other countries for the treatment of patients with Parkinson's disease (PD) who are receiving levodopa/L-DOPA (LD) therapy (with or without a peripheral decarboxylase inhibitor) and who are experiencing deterioration in their therapeutic response to LD. Selegiline is thought to exert its therapeutic effect via inhibition of the monoamine oxidase (MAO) B enzyme and the decrease in dopamine metabolism and turnover. Selegiline is marketed in the U.S. as Eldepryl®, a formulation that is swallowed.

Zydys selegiline (ZS) is a rapidly-disintegrating oral dosage formulation of selegiline consisting of an open matrix of water-soluble ~~_____~~. This formulation disintegrates quickly (e.g. beginning within seconds) in saliva on the tongue, releasing selegiline into the saliva, and does not require added water to aid disintegration, dissolution or absorption. Major theoretical advantages of the ZS formulation include : 1) improved patient compliance with the easily administered tablet that rapidly dissolves on the tongue, especially for patients with swallowing difficulties; 2) reduced variability in absorption relative to orally-administered standard tablets, with potentially more predictable clinical effects; and 3) reduced overall exposure to selegiline and metabolites (based on administered dose), and reduced production of potentially active metabolites.

b(4)

The original IND (47005) for ZS was submitted to the FDA in 1994 by RP Scherer DDS. Eventually this product was sold to Elan Pharmaceuticals who submitted an NDA (21479) to the Agency on 4/8/02. On 2/7/03, an approvable letter was issued to the sponsor (Elan) noting 2 main clinical concerns (conduct a tyramine sensitivity study and conduct a QTc study) among several other concerns of other disciplines. During the interim, Elan sold this product to another sponsor (Valeant Pharmaceuticals). There have also been interactions between the division and sponsor to provide advice to the sponsor. Most notably, there was a face to face meeting (5/25/04) with Valeant and the DNDP to discuss the study design for the tyramine sensitivity study and the QTc study. The sponsor did not follow much of the advice of the DNDP and markedly altered its study design for the tyramine sensitivity study subsequent to the 5/25/04 meeting. The DNDP had a teleconference with the sponsor to provide additional advice on the tyramine sensitivity study but the sponsor did not inform the DNDP that the tyramine sensitivity study had already been completed at the time that the DNDP was giving advice about how to conduct the study. The sponsor submitted (received 12/16/04) a Response to the Approvable Letter by the new sponsor but this application was not filed because of deficiencies (significant deficiencies and problems related to the navigability of the application, no requested re-analysis of oropharyngeal adverse events, and other more minor ones). The sponsor's response was re-submitted and received by the Agency on 3/20/05 and this response is the subject of this review.

This Executive Summary is organized by presenting a Clinical Comment from the Approvable letter, followed by the Sponsor's Response, followed by Reviewer Comments. I have provided a brief summary of the tyramine and QTc study designs immediately before the presentation of the respective Clinical Comment requiring the study.

Tyramine Sensitivity Study Design

The sponsor was informed that it needed to conduct a tyramine sensitivity because results of the previous tyramine sensitivity studies were not judged to be reliable. The sponsor conducted a tyramine challenge sensitivity study assessing the effects of 2.5, 5, and 10 mg daily ZS dose groups compared to placebo and phenelzine (15 mg BID, non-specific MAO inhibitor, positive control) in a randomized, double-blinded, placebo-controlled study in which healthy subjects were randomized to the parallel treatment groups. Subjects were challenged with increasing doses of tyramine (25 - 400 mg) at baseline/pre-treatment until subjects showed a threshold response (single ≥ 30 mm Hg increment in SBP). Subjects who showed such a threshold response (≥ 15 mm Hg on 3 consecutive measurements) to tyramine were randomized to one of the 5 treatment groups and were similarly studied for their tyramine threshold response (at least single increment in SBP of ≥ 30 mm Hg) after 11 days treatment.

FDA Clinical Comment in Approval Letter : Need to Conduct Tyramine Challenge Study Assessing Pressor Responses

“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 Zydys 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.”

Valeant Response to Comment : Contradictory results from tyramine challenge Studies

We acknowledge that the results from the prior tyramine-challenge studies are not in full agreement with that published in the medical literature, at least in part due to the study design and lack of adequate controls. Rather than attempt to explain the differences between these studies, we have conducted a new Phase 1 Clinical Study “A Phase 1 Study in Healthy Subjects to Evaluate the Effect of Steady-State Doses of ZELAPARTM (Zydys® Selegiline HCl) on Blood Pressure Responses to Tyramine” (Protocol RNA-ZEL-B21-102) to

address the tyramine-pressor effects of ZELAPAR TM (Zydis®-selegiline) compared to an active control, NARDIL®. The key pharmacodynamic results of that study are summarized and discussed below.

- This study was a robust evaluation of the potential for ZELAPAR TM to interact with tyramine. The results demonstrate that the clinically recommended dose of ZELAPAR TM 2.5 mg once daily is similar to placebo with regard to its effect on the tyramine pressor response at steady state.
- The active control drug (NARDIL 30 mg) demonstrated a clear positive effect on tyramine pressor response that was comparable to the published results and this effect was substantially higher than that observed with the clinically recommended 2.5 mg ZELAPAR dose. ZELAPAR, at an intermediate dose of 5 mg and at a supratherapeutic dose of 10 mg daily, was shown to enhance the tyramine pressor effect, but the level of effect observed following the 5 mg dose was clinically and statistically significantly lower than that observed with NARDIL 30 mg.
- At two supra-therapeutic doses of 5 mg and 10 mg daily, there was an enhanced tyramine pressor effect, but the effect observed following the 5 mg dose was clinically and statistically significantly lower than that observed with NARDIL 30 mg.

Reviewer Comment

- In general, I agree with the sponsor's above response and comments.
- The data show that the higher doses (5 and 10 mg daily) of ZS showed an increased sensitivity to tyramine relative to increased pressor responses. However, none of the ZS doses (2.5, 5, or 10 mg daily) seemed capable of producing a sustained threshold pressor response (≥ 30 mm increase systolic blood pressure) after challenge with increasing tyramine doses up to 100 mg under fasting conditions more frequently than placebo-treated subjects. In contrast, a substantial percentage of subjects (15 % challenged with 25 mg tyramine and 62 % challenged with 100 mg tyramine) treated with the positive control (phenelzine, non-selective MAO inhibitor) showed sustained threshold pressor responses (2 consecutive ≥ 30 mm increments of systolic blood pressure) after challenge with increasing tyramine doses up to 100 mg under fasting conditions more frequently than placebo-treated subjects (0 %).

A "high" tyramine content oral challenge from food and/or drink is considered to be probably in the range of 40-50 mg tyramine. In addition, administration of a tyramine challenge added to food can be associated with decreased bioavailability of tyramine (including decrease C_{max} , AUC and delayed T_{max}) and decreased pressor responses depending on various conditions. Given that the fasting tyramine study challenge would appear to represent a tyramine challenge under a worst case scenario that could be experienced by eating and/or drinking food or liquid containing 100 mg of readily bioavailable tyramine, I interpret these results as suggesting that none of the daily ZS treatments (2.5, 5, or 10 mg) appear to be associated with a significant risk for a tyramine-induced hypertensive "cheese" reaction. The

ZS dose to be approved would be 2.5 mg. The fact that none of the higher doses of ZS (5 and 10 mg daily) appeared to be capable of inducing sustained pressor responses suggests a reasonable margin of safety with respect to a hypertensive risk for patients who might experience a significantly increased pharmacokinetic (PK) exposure (up to an equivalent dose of 10 mg daily) for some reason.

- The sponsor did not conduct a fasting tyramine challenge study as we had recommended (particularly including additional doses at small increments up to 800 mg day and inclusion of a treatment group taking conventional swallowed selegiline 5 mg BID for comparison). Nevertheless, I think that the sponsor's results are adequate and allow us to address the question of whether these doses of ZS appear to be associated with a significant risk for a tyramine-induced hypertensive "cheese" reaction. This most recent study suggested that there appears to be an increased frequency for observing "threshold pressor responses" when a single isolated threshold pressor response is used as the criterion for a threshold response rather than requiring > 2 consecutive blood pressures to achieve the criterion. In retrospect, I consider that results of the sponsor's previous "definitive" fasting tyramine challenge study (AN17933-101) were erroneous and suggested that subjects showing tyramine-induced threshold pressor responses likely represented false positive responses.

QTc Study Design

The sponsor was informed that it needed to conduct a QTc study to characterize or exclude QTc prolongation related to ZS treatment. One randomized, double-blinded, placebo-controlled study showed a mild QTc prolongation associated with ZS treatment when the QTc at the end of the study was compared to the baseline/pre-treatment QTc and results of placebo-treated patients and another identical study did not show such a change.

The sponsor conducted a "thorough" QTc study assessing the effects of 2.5 and 10 mg ZS dose groups were compared to placebo and moxifloxacin in a randomized, double-blinded, placebo-controlled study in which healthy subjects were randomized to the parallel treatment groups. A 12 lead Holter monitor was used to collect electrocardiographic data. Subjects were studied at baseline by collecting 3 ECGs over a short interval at 12 different times over 24 hours and then repeating this ECG collection after treatment on day 12, presumably at PK steady state for ZS.

FDA Clinical Comment in Approvable Letter : Need to Conduct Thorough QTc Study

Clinical Comment : "As with 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."

Valeant Response to Comment: Effect of Selegiline on QTc Prolongation

Although Elan Pharmaceuticals presented an explanation of the inconsistencies in QTc results from Studies 025 and 026, as summarized in _____ analysis, submitted in the August 7, 2003 amendment to the NDA, Valeant agreed to conduct a definitive QTc study entitled, "A Negative and Positive Controlled Evaluation in Healthy Male and Female Subjects of the Potential for ZELAPAR (Zydis® selegiline HCl) at Steady-State to Affect ECG Parameters with Special Emphasis on Cardiac Repolarization" (Protocol RNA600301-101), in accordance with discussions with the Division. The results of that definitive study are reported below. b(4)

- The mean maximum on-treatment values for all ECG parameters were within the normal range for all treatment groups. No apparent differences between treatment groups were evident for HR, RR, PR, or QRS. The mean maximum changes from baseline achieved in the ZELAPARTM treatment groups for QT parameters was consistent with those observed for placebo, and less than the mean maximum changes from baseline QT and QTc demonstrated in the moxifloxacin group.

- The maximum change from baseline for QTcI was an increase of approximately 18 msec and 17 msec in the 2.5 mg ZELAPARTM and 10 mg ZELAPARTM groups, respectively, compared to 17 msec in the placebo group and 23 msec in the moxifloxacin group. The increase in QTcI from baseline elicited by administration of moxifloxacin was significantly different from the change from baseline QTcI in the ZELAPARTM treatment groups or placebo. These results validated the sensitivity of this study to detect small changes in QTc intervals.

- Neither the 2.5 mg ZELAPARTM group nor the 10 mg ZELAPARTM group were significantly different from placebo with respect to on-treatment changes in QTcI, nor was any significant difference detected between the two ZELAPAR treatment groups.

Reviewer Comment

- Considering all these results and analyses, critical questions to be answered ultimately are :

- 1) Does ZS treatment prolong QTc relative to placebo?

- 2) Is there a gender difference in the magnitude of ZS-related QTc prolongation relative to placebo?

- 3) If there is a suggestion of a ZS-related QTc prolongation relative to placebo, is there any clinical concern relative to an approval action or labeling based upon the magnitude of the suggested QTc prolongation?

- **Considering all these results and analyses, I still cannot answer question # 1 definitively by noting that ZS does or does not prolong QTc relative to placebo. Although I agree that this study did not show any statistically significant increments in**

QTc for ZS relative to placebo, I interpret this “thorough” QTc study as being a “positive” study because it did not exclude a possible increase in QTc below 10 msec. The conservative ANCOVA analysis (using Dunnett’s test) showed that the upper bound of the 95 % CI (one-sided) was ~ 11 msec and the QTc guidance says that the largest time-matched QTc increment of the change from baseline should exclude 10 msec for this upper boundary to be called a “negative” study that excludes this value as a potential risk and that the largest, placebo-corrected, time-matched mean QTc change from baseline should be < 5 msec.

I have raised the question whether there are mild QTc increments in QTc at 3 and 12 hours in all subjects treated with high dose 10 mg ZS. If so, the largest mean treatment effect (placebo-corrected) was ~ 5-7 msec (for all 3 QT corrections) at 12 hours. Thus, we still do not know if ZS prolongs QTc and have not been able to exclude a risk of 10 msec.

- My answer to question # 2 is that there are data that raise the suspicion of a different gender effect of high dose 10 mg ZS on QTc prolongation based upon mean results and CIs not associated with statistical significance. The gender analyses raise the question of possibly greater numerical QTc prolongation at 3 hours in males (vs females) and a substantial mean QTc increment (~ 10 msec) at 12 hours only in females. I am not aware of other drug results that show such a gender difference of QTc prolongation occurring at a certain time only in one gender and not in the other gender. It is difficult to know whether these possible gender differences are or are not real. Of note, the gender analyses were based upon approximately half the number of subjects (~ 20) of that (~ 40) analyzed in the full analysis of all subjects.

It is also possible that the apparent gender effects raised are an artifact of multiplicity (i.e. making multiple statistical comparisons such as 3 paired treatment comparisons on 12 occasions; total 36 statistical comparisons).

- In answering question # 3, I note my thoughts about approval and labeling with certain caveats. At this time I think that it is a fair perspective to say that ZS could produce relatively small QTc increments that were not statistically significant but are possible because a margin of 10 msec was not able to be excluded in the “thorough” QTc study. These possible increments by themselves do not necessarily raise serious safety concerns if one would assume that ZS exposure would not exceed that associated with 10 mg daily ZS treatment in a healthy subject (~ fold Cmax and AUC of that expected in healthy subjects treated with 2.5 mg daily, the recommended dose). However, I have concerns that potentially much higher selegiline exposures could be experienced and these significantly higher exposures could potentially be associated with significant QTc prolongation and thus a risk of Torsades des pointes which can be fatal. My concerns about this risk in the face of markedly increased exposures to selegiline are based upon 3 considerations : 1) a published study showing that patients with hepatic impairment had a mean increased AUC and Cmax that were 18 fold and 7 fold respectively greater than those of healthy subjects and patients with renal impairment had a mean increased AUC

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.

Valeant Response to Comment : Effect of Selegiline on Resting and Orthostatic Blood Pressure

As part of the Tyramine-Challenge Clinical Pharmacology Study, Valeant did investigate the effect of selegiline (following ZELAPARTM administration) on resting and orthostatic blood pressure during the conduct of the Tyramine-Challenge study (Study RNA-ZEL-B21-102). The results of that study are summarized below.

- There were no changes in orthostatic BP related to timing of dose.
- The change in orthostatic SBP on treatment relative to the pre-randomization baseline was variable and no trends were apparent between treatment groups or within treatment groups with respect to time after dosing.
- The mean change from baseline orthostatic SBP at scheduled time points over the 24-hour post-dose assessment period ranged from -5.7 to 3.2 mmHg for 2.5 mg ZELAPAR TM, from -3.6 to 2.4 mmHg for 5 mg ZELAPARTM, and from -4.5 to 4.4 mmHg for the 10 mg ZELAPARTM dose, with no discernable pattern to the values.

Reviewer Comment

- I agree with the sponsor's response that the study of orthostatic blood pressure responses did not show a clear effect on orthostatic blood pressures indicating orthostatic hypotension related to ZS treatment compared to placebo treatment.
- The sponsor has also analyzed these data for categorical increments blood pressure (SBP \geq 20 mm Hg and/or 10 mm DBP \geq 10 mm hg) in supine, standing and orthostatic positions. There is no real suggestion of ZS-induced categorical increments in blood pressure timed to dosing for ZS relative to placebo. A question of ZS related increments in blood pressure had been raised in the previous 101 study in which ZS was compared to Eldepryl (10 mg QD) but in which there was no placebo group.

QUESTION POSED BY CLINICAL REVIEWER DURING REVIEW ABOUT EFFECT OF RENAL AND HEPATIC IMPAIRMENT ON ZYDIS SELEGILINE PHARMOCOKINETICS

FDA:

Why should there not be a concern now that people with various degrees of hepatic and/or renal impairment who take 2.5 mg daily Zydys selegiline will not experience a markedly increased plasma exposure of selegiline that could be associated with an increased tyramine

sensitivity (i.e. possible risk of hypertensive, "cheese" reaction)? We know that conventional selegiline loses its MAO-B selectivity (i.e. exhibits progressively increasing inhibition of MAO-A) as dose/exposure of conventional selegiline increases and that there is increased sensitivity to tyramine. Your data also shows that there is increased sensitivity to tyramine for blood pressure responses with high dose Zydys selegiline.

Sponsor's Response:

The data submitted in this application does establish that ZELAPAR™ (ZYDIS® selegiline), at the clinically recommended dose (2.5 mg daily) has a reasonable safety margin for tyramine-induced increases in blood pressure. As the reviewer notes, there is increased sensitivity to tyramine at a dosage of 10 mg daily of ZELAPAR™, suggesting some loss of MAO-B selectivity at 4-times the recommended dose.

In a recently published study (Anttila et al., 2005) 10 patients with liver disease, 10 patients with renal disease, 10 patients receiving hepatic enzyme inducers, and 10 healthy controls received a single 20 mg oral dose of conventional selegiline (ELDEPRYL®) [2-4 times the usual single dose] and the pharmacokinetics of selegiline and its metabolites were measured for 48 hours after dose administration. Relative to the healthy controls, patients with "chronic liver disease" had a 7-fold increase in mean selegiline C_{max} and an 18-fold increase in mean selegiline AUC.¹ The study also demonstrated a 4-fold and 6-fold increase in mean selegiline C_{max} and AUC, respectively, in 10 patients with "impaired kidney function". Unfortunately, the degree of hepatic or renal impairment could not be assessed as the limited baseline laboratory results in the impaired groups overlapped the normal range up to 3-4 times the upper limit of normal, and the study participants were not stratified by degree of impairment. Baseline values (means, individual results, or ranges) for serum albumin, serum bilirubin, INR or prothrombin time were not reported for the population with hepatic disease; and the presence or absence of ascites or other signs and symptoms was not mentioned. No values for creatinine clearance or other measures of GFR were reported for the group with renal impairment.

Examination of the individual plasma concentration versus time curves presented in the publication (figure 2) suggests that many of the subjects with liver impairment or renal impairment had plasma concentrations that were very similar to the control subjects. While the results of this study raise concerns that some individuals with hepatic or renal disease had substantial increases in selegiline exposure, others were largely unaffected and the relationship between disease severity and impairment of drug clearance is undefined. There were no reported adverse events in any participant nor any clinically relevant changes observed in post-study laboratory test results.

In light of the data quoted above, one cannot exclude the possibility that renal or hepatic impairment might increase systemic exposure of selegiline to levels outside the safety margin for increased tyramine sensitivity. Since the pharmacokinetics of ZELAPAR™ (ZYDIS® selegiline) and its metabolites have not been evaluated in patients with hepatic or renal insufficiency, it is not presently known to what extent the systemic exposure of selegiline is affected by varying

degrees of renal and/or hepatic dysfunction. It should be further noted that selegiline following Zelapar administration is principally absorbed through the buccal route. This results in lower first-pass metabolism and hepatic impairment may have a lesser influence on the systemic selegiline levels. Valeant has agreed with the Agency to conduct pharmacokinetic studies of ZELAPAR™ in hepatic and renal impairment as Phase 4 commitments.

Until the results of definitive studies are available to support recommendations regarding the use and possible dose adjustments of ZELAPAR™, the Sponsor recommends that the following warning be included in the Zelapar package insert and that the package inserts for existing selegiline formulations should also be modified with this wording:

[Redacted text block]

b(4)

Reviewer Comment

- I agree essentially with most of the sponsor's comments on this study. This study raises serious questions about how renal or hepatic impairment may significantly increase exposure both Cmax and AUC. Of interest, it seems that exposure of only selected patients is substantially increased and that exposure in many seems unaltered.

A major problem with interpreting the significance of this study is the fact, as noted by the sponsor, that the degree of impairment for enrollment in this study is not clearly characterized. Thus, we are not able to assess how these effects might be experienced in patients in whom we typically characterize the degree of impairment according to particular criteria as mild, moderate, or severe. The enrollment criteria did not seem very quantitatively specific. Of interest, the mean serum aminotransferase (AST, ALT) levels of hepatically impaired subjects were increased approximately 2-3 fold of the mean of the controls, and the mean BUN and creatinine of renally impaired subjects were approximately 2.5 fold of mean levels of controls. Impaired subjects in the hepatic group had a diagnosis of liver dysfunction "confirmed histologically" and renally impaired subjects had "stable long-term renal impairment with elevated serum creatinine values." In addition to the curves showing large variability in exposures, the SD for each mean AUC is very large and greater than the mean similarly reflecting the impression from visualizing individual subject exposure.

- From a PK perspective, there are also some study design issues that make me question their relevance to the application under review. The standard dose of conventional, swallowed selegiline is 10 mg daily (5 mg BID). In this study patients were administered a single dose of 20 mg selegiline and data that were collected were not at steady state. Ideally, it would have been potentially more relevant for us to know what is the effect of either impairment on an approved dose (5 mg BID) and at steady state which is reached after several days of multidosing administration. I question whether similar quantitative effects (e.g. 18 and 6 fold increase in AUC exposure and 7 and 4 fold increase in Cmax in hepatic and renal

impairment, respectively) would have been observed if selegiline had been administered as 5 mg BID and assessed at steady state.

- Following my review of this publication, I contacted Charlene Flowers in the Office of Drug Safety (ODS) and requested a specialized search of the Adverse Event Reporting System (AERS) data base, a repository for MedWatch Reports, to identify case reports of various adverse events in patients with underlying renal or hepatic disorder/impairment. Unfortunately, a wild card search of AERS utilizing selected hepatic% and renal% terms in the descriptive event and relevant medical history fields was limited by abbreviated words, misspelled words, or foreign jargon. Ultimately, we were unsuccessful at identifying the population of interest. When a typically search of AERS with terms indicative of associated renal or hepatic impairment is conducted the results identify patients who experienced renal/hepatic impairment subsequent to the temporal administration of selegiline. Thus, we do not know how frequently patients with adverse events associated with selegiline treatment had associated renal or hepatic impairment without reading and analyzing individual MEDWATCH reports.
- Although there are problems/limitations/shortcoming of this study, I think that it is difficult to ignore the findings in this study. These findings in this publication are contradictory to the impression one would get from the uncontrolled (no unimpaired hepatic or renal control group within the study) study of transdermal selegiline in another NDA. If there really is an increased exposure associated with either impairment (and the renal seems more difficult to accept considering the supposedly low excretion by kidney), then patients could be at a potentially serious risk for adverse reactions, perhaps the most serious being a hypertensive "cheese" reaction from loss of the relative selectivity for MAO-B. I do not think that the sponsor's cautionary advice for the label is very practical or helpful. I also note that the fact that our Clinical Pharmacology reviewers think that 2 separate studies should be conducted in patients with hepatic and renal impairment leads me to believe that neither can they dismiss the possible implications or significance of this recent publication.

One approach could be to disregard these findings and request that the sponsor conduct phase 4 studies assessing effects of renal and hepatic impairment and not mention anything in the label or perhaps mention something about these findings and craft some type of precautionary statement. This would seem difficult without knowing what to say about specific degree of impairment. One could entertain this argument considering that selegiline has been approved and used for many years and we do not have a clear suggestion of increase risk for adverse events with either impairment. The contradictory results of the transdermal selegiline studies would seem to support this approach along with concerns about the results in the publication itself. An alternative approach could be to contraindicate selegiline use in patients with renal or hepatic impairment but again it would seem difficult to craft language describing how this impairment is defined. Finally, the most conservative approach would be to require that the sponsor conduct both of these studies prior to approval because it is not acceptable to allow this risk for this new formulation.

b(5)

Reviewer Conclusions

1. ZS at 2.5 mg daily is an effective dose for the sponsor's desired indication/claim. The sponsor did not adequately study the 1.25 mg daily dose to receive a claim for this dose.
2. **I have concerns about the potential safety of ZS 2.5 mg daily if patients treated with this dose have various conditions (e.g. hepatic impairment, renal impairment, concomitant sex steroid treatment, concomitant treatment with a drug providing increased exposure via a drug-drug interaction (DDI) with important CYP^b metabolizing enzymes of ZS) that could markedly increase selegiline exposure.** My concerns are most pointedly directed at the risk of a hypertensive "cheese" reaction at very high multiple exposure of ZS 2,5 mg , and possible QTc prolongation and corresponding risk of Torsades des pointes (that can be fatal) because the QTc study is "positive" and did not exclude a possible QTc prolongation below 10 msec.

My concerns about this risk in the face of markedly increased exposures to selegiline are based upon 3 considerations : 1) a published study showing that patients with hepatic impairment had a mean increased AUC and Cmax that were 18 fold and 7 fold respectively greater than those of healthy subjects and patients with renal impairment had a mean increased AUC and Cmax that were 6 fold and 4 fold respectively greater than those of healthy subjects; 2) a publication showing administration of several single doses of oral conventional selegiline was associated with markedly increase exposures (e.g. 22 fold increased AUC and 11 fold increased Cmax for 10 mg selegiline; the approved daily dose); and 3) I am not convinced that we are confident that markedly increased exposures (AUC and/or Cmax) are not possible from DDIs from other drugs altering the metabolism of selegiline by direct inhibitory actions or by indirect competitive antagonistic/inhibitory actions on important CYP enzymes involved in the metabolism of selegiline. I do not necessarily find it reassuring that we are not aware of serious safety risks from these potential interactions in patients who are taking conventional oral selegiline (Eldepryl).

Very recently, a more detailed Clinical Pharmacology/Biopharmaceutical review (9/21/05), that addressed the publications stimulating concern about increased selegiline exposure and publications characterizing CYP enzymes in selegiline metabolism was completed. This review noted that the understanding about the CYP enzymes involved in selegiline metabolism is not very clear. Thus, not only do we NOT have a clear understanding of which CYP enzymes play an important, major role in selegiline metabolism, the full complement of which CYP enzymes are involved in selegiline metabolism has not been clearly established. In the absence of this critical information, it is not possible to recognize and understand the potential for various DDIs (e.g. especially by direct CYP enzyme inhibition or indirect antagonistic/competitive CYP enzyme inhibition). This critical information is most relevant to this NDA because markedly increased selegiline exposures can markedly increase safety risks for tyramine-induced hypertensive "cheese" reactions, possibly QTc prolongation/Torsades des pointes, and other dose-related selegiline toxicities. —

b(5)

3 SPONSOR'S COMPLETE RESPONSE TO THE LAST APPROVABLE LETTER

3.1 Reviewer's Overview of Organization and Approach of Clinical Review

The sponsor quoted language from the DNP's last Approvable letter and then responded by addressing each issue. I have organized my review to show the concluding views of each party (sponsor, Clinical Pharmacology reviewer, this clinical reviewer) involved in this assessing the response to the last approvable letter. More specifically, I have provided the DNP comment regarding each issue, followed by the sponsor's summary and/or conclusion about the issue, followed then by the Clinical Pharmacology reviewer's conclusions (and in some instances comments), and finally by my conclusions (and in some instances comments). I have also provided the Clinical Pharmacology reviewer's recommendations including phase 4 commitments that should be obtained.

I have reviewed the sponsor's responses including the information supporting the response and the sponsor's conclusions. However, my review has primarily focused on the summary comments and conclusions of the Clinical Pharmacology reviewer (Dr. Veneeta Tandon) after her review of the sponsor's Complete Response. Because Dr. Tandon's review provides detailed information submitted by the sponsor, I have not repeated this information in my review. If interested, the reader can refer to the finalized review of Dr. Tandon for a description of the sponsor's detailed response.

3.2 FDA Comment 1 – CYP450 and Selegiline Metabolism (Letter Pages 1-2, last para. Page 3)

"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."

“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.”

3.2.1 Sponsor’s Conclusion

“Based on results obtained from *in vitro* studies using cDNA expressed CYPs, human liver microsomes and human pharmacokinetic studies, we can conclude that CYP2B6 and CYP3A4 are involved in the metabolism of selegiline to desmethylselegiline and methamphetamine in humans. However CYP2A6 may also play a minor role in the metabolism of selegiline.”

The sponsor had conducted and submitted results of a new *in vitro* study investigating cDNA CYP 450 enzymes in selegiline metabolism in addition to reviewing the published literature in detail.

3.2.2 Clinical Pharmacology Reviewer Summary Comments and Conclusions

“Reviewer’s Comment:

- Highest dose of itraconazole (400 mg) has not been used in this study.
- On the face value this study seems adequately conducted. However, it is known that single doses of selegiline are not predictive of multiple dose levels and a single dose selegiline study may not truly represent the steady state selegiline levels.”

“Overall Conclusions on ISSUE 1:

The sponsor has adequately characterized the *in vitro* metabolism pathway of selegiline and has found the following:

Major pathway of selegiline metabolism are: CYP 2B6 and CYP 3A4
Minor pathway of selegiline metabolism is: CYP 2A6

This information should be included in the label.

Summary of Reviewer’s thoughts:

Facts:

- *In vitro* CYP 3A4 was not major pathway, except that it is abundant *in vivo*.

3.3 Clarification of the Effect of Oral Contraceptives and Hormone Replacement Therapy (HRT) on Selegiline Metabolism

3.3.1 Sponsor's Conclusion

"In summary, there is no evidence of a clinically relevant effect of female sex steroids used in HRTs marketed in the United States on the pharmacokinetics of selegiline. However, depending on the CYP2B6 phenotype expression and the dosages of steroids administered, i.e. particular estradiol and ethinyl estradiol, a mild effect of HRTs on the selegiline pharmacokinetics can not be completely ruled out, although any effect is expected to be less significant for selegiline administered as Zelapar™ than for selegiline administered as conventional tablets."

3.3.2 Clinical Pharmacology Reviewer Conclusions

"Overall conclusions from ISSUE 4:

- Only the literature article by Laine et. al, 1999 suggests a strong interaction between selegiline and gestodene 75 µg/ethinyl estradiol 30 µg combination (N=4). The same dose and combination of oral contraceptive (Palovaara et al, 2000) did not show a significant interaction with midazolam. Gestodene is a potent CYP 3A4 inhibitor, midazolam a strong substrate, selegiline is also a substrate of CYP 3A4 and CYP 2B6. So, ideally the effect of gestodene on CYP 3A4 substrate midazolam and selegiline should be similar.
- 2 mg Estradiol valerate and 250 µg levonorgestrel (HRT) seemed to inhibit the CYP 2B6 mediated hydroxylation of bupropion (47%), a strong CYP 2B6 substrate (Palovaara et al, 2003). Neither of these are known inhibitors of CYP 3A4 or CYP 2B6. Hence, mechanistic basis of this interaction is unclear. In this study subjects on oral contraceptive (OC):30 µg ethinyl estradiol and 150 µg desogestrel inhibited the hydroxylation to a lesser extent (31%) The author suggests that patients receiving HRT and OC may need dosing adjustment when treated with drugs that are metabolized by CYP 2B6.
- Estradiol valerate and levonorgestrel (HRT) combination at the same dose as in the bupropion study did increase the AUC of selegiline by 59% without affecting the levels of the metabolite: which also seems strange, unless some other metabolic pathways are affected (Palovaara et al, 2002).

These changes were not statistically significant probably due to the high intersubject variability.

- Therefore, there is no strong evidence of an interaction with HRTs and selegiline, however a mild effect of estradiol and ethinyl estradiol in particular cannot be completely ruled out. It should be noted that gestodene is not marketed in the US.
- Additional studies are not warranted because:
 - Gestodene is not marketed in US, so a repeat of the Laine study for verification of the results cannot be recommended.
 - Mechanistically only ethinyl estradiol is a weak inhibitor of CYP 3A4 and CYP 2B6. Ethinyl estradiol 30-35 µg is the oral contraceptive dose. Given the patient population an oral contraceptive study may not be justified. The dose of ethinyl estradiol for HRT is 2.5 µg, much lower than the OC dose (only present in one HRT product: FEMHRT). Hence a HRT drug interaction study using ethinyl estradiol as a component cannot be recommended due to its low dose.
 - 2 mg Estradiol valerate and 250 µg levonorgestrel (HRT) combination with selegiline has already been evaluated by Palovaara et al. Although a 59% increase in selegiline exposure was observed this increase was not statistically different. Given the high intersubject variability of selegiline a repeat of this study is also not warranted.

(Note to the Medical Officer: If the epidemiology data shows that Parkinson's Disease is prevalent in patients less than 45 years as well, then a drug interaction study with oral contraceptive dose of ethinyl estradiol may be recommended)

3.3.3 Clinical Reviewer Comments

- The Clinical Pharmacology review made a note to the Medical Officer suggesting that it may be desirable to conduct a drug-drug interaction study of an oral contraceptive dose of ethinyl estradiol with selegiline "if the epidemiology data shows that Parkinson's Disease is prevalent in patients less than 45 years."

A recent publication (Van den Eden et al., Am J Epidemiology, 157 : 1-15-22, 2004) suggested that the incidence of Parkinson's Disease in females is very rare in women < 40 years of age, and although more common, still relatively rare (~ 1 %) in females < 50 years of age. Furthermore, I asked the sponsor to analyze the enrollment age of patients

3.4 Potential for Selegiline as an Inhibitor of CYP 450 Enzymes

3.4.1 Sponsor's Conclusion

"The inhibitory potency of selegiline has been reported by Taavitsainen et al (2000). IC₅₀ values for CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4 were 350 μM or higher, indicating that selegiline is highly unlikely to inhibit most CYP450 enzymes. The IC₅₀ for CYP2C19 was 21 μM. However, clinically effective systemic levels of selegiline remain in the low nanomolar range and micromolar concentrations would be required to inhibit CYP2C19. Hence, it is highly unlikely that any interaction would arise by this mechanism."

3.4.2 Clinical Pharmacology Reviewer Conclusion

"Selegiline is not an inhibitor of CYP 450 at therapeutic concentrations. This was also concluded by the previous OCP reviewer, Dr. Andre Jackson."

3.4.3 Clinical Reviewer Conclusion

- I concur with the Clinical Pharmacology reviewer's conclusion that selegiline does not appear to inhibit CYP 450 enzymes.

3.5 Potential for Selegiline as an Inducer of CYP 450 Enzymes

3.5.1 Sponsor's Conclusion

“In conclusion with respect to metabolism of Zelapar™, we believe that the literature referenced in the approvable letter, together with the updated literature referenced in this response and our recent *in vitro* studies have adequately elucidated the pathways of selegiline metabolism. The major CYP isoenzymes involved in the metabolism of selegiline are CYP2B6 and CYP3A4, while CYP2A6 may play a minor role in the metabolism of selegiline. Except for gestodene, none of the contraceptive and hormone replacement therapies has a significant drug interaction potential with selegiline. Selegiline is neither an inhibitor nor inducer of CYP450 enzymes. We believe no further studies are required regarding the enzymes responsible for the metabolism of selegiline. We will include statements in our package insert defining the role of CYP450 enzymes in the metabolism of selegiline, indicating that selegiline is neither an inhibitor nor inducer of CYP450 enzymes, and that there is a lack of drug interactions between selegiline and hormone replacement therapies available in the United States.”

3.5.2 Clinical Pharmacology Reviewer Conclusion

The induction potential of selegiline is not adequately characterized. This *in vitro* study should be requested as a Phase 4 commitment.

3.5.3 Clinical Reviewer Conclusion

- I concur with the Clinical Pharmacology reviewer’s conclusion that the induction potential of selegiline has not been adequately characterized and that an *in vitro* study should be requested as a Phase 4 commitment.

3.6 FDA Comment 2 – Effect of Hepatic and Renal Impairment on Selegiline Plasma Concentrations (Letter Pages 2-3)

“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."

3.6.1 Sponsor's Conclusion

"Overall Summary

From a scientific and medical perspective, including a lack of a clear identified signal from the selegiline clinical and post-marketing safety databases, Valeant has demonstrated that the use of the buccally absorbed Zelapar tablets in patients with hepatic and renal disease can be prescribed

safely and not result in unacceptable clinical consequences. However, we recognize that there is a small fraction who have severe disease and who are undiagnosed and asymptomatic, estimated at 0.1-0.5% for patients with hepatic impairment and 1.3% for patients with renal impairment, that may be at higher risk of elevated selegiline levels. Acknowledging this possibility, even though we have found no correlation between selegiline levels and adverse events or discontinuations, we are proposing the following language be added in the package insert: "Zelapar should be used with caution in patients with a history of or suspected _____renal or hepatic disease". This will provide the appropriate instruction to physicians so they can manage any potential risk of Zelapar use in Parkinson's disease patients with hepatic and renal impairment.

b(4)

Accordingly, we believe it is prudent and reasonable to allow Zelapar™ to be available for use in treating patients with Parkinson's disease and that the planned hepatic and renal impairment studies to be returned to a Phase 4 commitment."

3.6.2 Clinical Pharmacology Reviewer Summary Comments and Conclusions

"Overall conclusions from ISSUE 5:

The Agency Medical Officer, Dr. Kapcala also was able to contact Antilla et al. and get additional information on the laboratory parameters determining the degree of liver and renal impairment in the subjects (such as serum albumin, serum bilirubin, AST, ALT levels for liver impairment assessment and urea and serum creatinine for renal impairment assessment of the subjects used in the literature study. In addition to this, individual subject PK parameters were also obtained from the authors.

For liver impaired subjects: All parameters (such as encephalopathy grade prothrombin time) for obtaining Child-Pugh classification for liver impairment was not available. Information available were serum bilirubin and albumin. Based on this there were only two subjects that could be categorized as severe. There was one subject with high AST and ALT levels. These subjects did not have the highest exposure to selegiline. Two of these subjects had high exposure to metabolites (DMS and L-MA), suggesting that liver impairment in these cases was not the most important contributing factor, otherwise these subjects may not have been able to make the metabolite. These subjects could have had renal impairment as well leading to high exposure of the DMS or on inducers. Though the authors of the paper state that the liver impaired subjects did not have any renal impairment and were not on any inducers. Also important to note is that the metabolite levels were not significantly different from those seen in normal volunteers.

What is also interesting to note is that the high AUCs of DMS and L-MA were not the subjects with the longest $t_{1/2}$, which adds on to the difficulty of interpreting the PK data.

Therefore, the subjects with the highest C_{max} and AUC of selegiline, had normal values of AST, ALT, serum albumin and borderline elevation of serum bilirubin. Based on this there does not seem to be a correlation between PK parameters and the level of impairment in the subjects evaluated.

For renal impaired subjects also no correlation could be determined with serum creatinine levels and PK parameters of selegiline and metabolites. About 44-58% of selegiline is eliminated mainly in the urine as metabolites, with up to 37% of the oral dose as L-MA. About 15% of the dose is also discharged in the feces. No unchanged selegiline has been detected in the urine. Given this, renal impairment should lead to increased levels of metabolites. The metabolite levels were 40-70% higher than the normal subjects. Given the inherent high variability in the pharmacokinetics of selegiline, these differences are not statistically significant.

Again in this case too, the subjects with high exposures were not the ones with longer half-lives.

Therefore, in general there are numerous inconsistencies in the Antilla paper that make the data uninterpretable.

However, we should not ignore the possibility of higher exposure in severe renal and hepatic impaired subjects, however, the available data are not scientifically sound; hence a pharmacokinetic study in the hepatic and renal impaired subjects is warranted.

The next issue is whether this study should be done prior to approval or as a Phase 4 commitment.

This reviewer recommends the studies be conducted as a Phase 4 commitment. The potential accumulation following oral buccally absorbed Zelapar™ will be much lower (estimated to be 3-5 fold by the sponsor, given the difference in metabolic ratios).

However, the overall safety from higher exposures at steady state (5-6 fold higher) with suprathreshold doses of 10 mg Zelapar (from tyramine challenge study, QTc study) should be evaluated by the Medical Officer.

Such accumulations were observed even upon multiple doses of Zelapar. Study 101 submitted in the original NDA showed that at Day 10, the AUC of selegiline was 3-4 fold higher than Day 1 for Zelapar 1.25 and 2.5 mg tablets. Study 96/014

showed that there was a 9-10 fold increase in AUC at Day 28. There is very high variability in the pharmacokinetic data for selegiline.

3.6.3 Clinical Reviewer Comments

- The publication noted that there did not appear to be any correlation between severity of hepatic or renal impairment and elevation of plasma selegiline exposure. I fully concur with this assessment based upon all the information that I have seen.

A significant limitation in the patients with liver dysfunction in this publication is that there was no classification according to the Child-Pugh categories as “mild,” “moderate,” or “severe” hepatic impairment. This classification is typically applied to cirrhotic patients to assess the level of surgical risk and is also often used for classifying patients to be studied in clinical pharmacology studies investigating the effect of various degrees of hepatic “impairment” on drug exposure. When considering hepatic functional impairment, it is critical to recall that elevated serum aminotransferase levels (e.g. serum ALT and/or AST) are poor indices of functional impairment but are considered better indices of liver injury than liver “function.” Although a variety of tests can be used to assess or reflect the level of hepatic “function,” more routine/standard laboratory tests that are considered to reflect impaired hepatic “function” better include increased serum bilirubin, prolonged/increased prothrombin time, and decreased serum albumin. The degree of abnormal alteration of these parameters can further reflect the severity of hepatic “impairment.”

When one looks at the serum bilirubin and serum albumin of subjects studied (see Clinical Pharmacology reviewer, Dr. Tandon’s review, Table 2, page 32), there is no good correlation between abnormalities of these parameters and plasma selegiline exposure. Serum albumin is within the normal range for all 10 subjects and the serum bilirubin was increased only in 4 subjects (2 of whom showed borderline elevation of 20 $\mu\text{mol/L}$ with normal being < 20). Of the 4 subjects with increased plasma selegiline exposure, only one showed a clear elevation (61) of serum bilirubin and another showed a borderline elevation of 20.

NOT FOR PUBLIC DISCLOSURE (bold text immediately below)

There was no information known about prothrombin time nor whether any subjects had ascites or encephalopathy (other parameters used for Child Pugh classification. Despite the fact that this information was specifically included in the publication, I had contacted the first author of the publication (Markku Anttila) and made specific inquiries about this information but he was only able to provide information on serum albumin and bilirubin. In addition, I had asked (via e-mail)

Markku Anttila to call me or give me a phone number to call me to try to discuss this study and possible reasons for the puzzling findings but he has not given me his phone number nor called me.

END OF NOT FOR PUBLIC DISCLOSURE

- I disagree with the sponsor's conclusive response shown below (in italics) here that indicates that increased plasma selegiline levels occur only in "those patients which had severe liver impairment."

"After contacting one of the co-authors of the Anttila et al (2005) study, _____ was informed that the 4 hepatic patients with the significantly elevated selegiline plasma levels relative to the normal control subjects had biopsy confirmed cirrhosis and marked impairment in liver function. This indicates that the increased selegiline plasma levels reported by Anttila et al (2005) were obtained only in those patients which had severe liver impairment, whereas the remaining 6 hepatic patients with a lesser degree of liver impairment had almost the same selegiline plasma levels than normal patients."

b(4)

I asked the sponsor specifically to provide information regarding who _____ (sponsor's consultant) had contacted and what specifically was communicated. The sponsor provided copies of the "string" of e-mails between _____ and the third co-author (Dr. Olavi Pelkonen). **My review of all of this e-mail correspondence does not find information/data supportive of the sponsor's contention disputed above here.** Of interest, some pertinent comments by Dr. Pelkonen note that "We did not perform Child-Pugh classification, but clinical markers can be found in the paper and they clearly show that the liver disease group differed from the others. On the other hand, I'd think that there was no really extremely severe liver condition in the group." Furthermore, _____ noted 2 assumptions : 1) "that the 4 subjects with the very high blood levels had histologically confirmed cirrhosis;" and 2) that the statement in the publication that increased selegiline levels was not correlated with severity of liver disease "was an attempt to correlate with liver chemistries and not histology." To this, Dr. Pelkonen responded : "this is true; all of them had histologically confirmed cirrhosis. Only one of those with histologically confirmed cirrhosis had pretty low selegiline max concentration."

b(4)

b(4)

I emphasize the fact that a subject had cirrhosis does not necessarily equate with the view that the subject also had significant hepatic impairment of hepatic "function." It is also clearly known that subjects can have significant impairment of hepatic "function" in the absence of cirrhosis and that it is not always easy to know the level of hepatic "function." I also emphasize that one of the 5 subjects with biopsy proven cirrhosis did not have any elevation of selegiline exposure.

Altogether considering all available information, it is not possible to explain precisely why the 4 subjects with elevated plasma selegiline exposure had this increased exposure and why the other 6 subjects did not. Thus, it is not clear whether : 1) the 4 subjects with

has only completed dosing in all subjects with moderate hepatic impairment and in only 1 of 6 subjects (planned) with mild hepatic impairment. The sponsor has also noted that the site at which the study was being conducted will no longer be participating and that it may be some time before this study is completed.

- It is also noteworthy that the level of renal impairment in most of the subjects was relatively minimal based upon the measurements of serum creatinine or BUN ((see Clinical Pharmacology reviewer, Dr. Tandon's review, Table 3, page 32). Of the 4 subjects with significantly increased plasma selegiline exposure (i.e. AUC), only one subject had a moderately increased serum creatinine elevation (~ 4 fold the upper limit of normal). In contrast, the other 3 subjects showed elevations that were less than 35 % above the upper limit of normal. When one looks at the BUN in these same subjects (BUN available only in 3), the BUN was normal in one, borderline increased in another, and moderately elevated in the subject with the greatest creatinine elevation. The BUN and creatinine of the other 6 subjects without significant increments in selegiline exposure clearly overlaps with the values of this with the increments in selegiline exposure.
- The results of the publication by Anttila et al are clearly puzzling and do not seem to make sense in terms of the inability to correlate increased selegiline exposure directly with the apparent level of renal or hepatic impairment. Nevertheless, I do not think that these results can be dismissed but rather consider them to be of potentially significant clinical safety import, and merit attention. Regardless, I think that it is possible to draft labeling that would be reasonably informative. I think that the following elements should be contained in the label;
 - 5) some subjects with renal or hepatic impairment may experience significantly increased plasma selegiline exposure based upon results of a publication;
 - 6) however the data in this publication did not permit one to draw conclusions about the degree/severity of renal impairment or the degree/severity of hepatic functional impairment;
 - 7) caution should be exercised in all patients with any degree of renal and hepatic impairment, especially patients with indices of functional hepatic impairment such as decreased serum albumin OR increased prothrombin time OR increased serum bilirubin);
 - 8) in practical terms, caution can mean considering discontinuing Zydys selegiline if a patient with any degree of renal or hepatic impairments seems to be experiencing adverse reactions in greater number, frequency, or severity than might ordinarily be expected (it is not practical to check plasma selegiline levels).
- Of potential relevance to this application, the sponsor responded to my specific inquiry

and informed me that the renal impairment PK study was nearly completed (only 5 of 6 subjects in the "severe" need to complete the study; other study groups including mild and moderate impairment dialysis patients and healthy matched subjects have completed the study). In contrast, the hepatic impairment PK study remains far from completed and has only completed dosing in all subjects with moderate hepatic impairment and in only 1 of 6 subjects (planned) with mild hepatic impairment. The sponsor has also noted that the site at which the study was being conducted will no longer be participating and that it may be some time before this study is completed. Although it may be some time, perhaps at least a year before the results of the sponsor's ongoing renal and hepatic impairment studies are available for updating the label, I think that adequate language can be drafted pending availability of these results.

- Finally, I will comment on some comments (shown in italics and quoted below) of the Clinical Pharmacology reviewer, Dr. Tandon, requesting evaluation by the Medical Officer.

"This reviewer recommends the studies be conducted as a Phase 4 commitment. The potential accumulation following oral buccally absorbed Zelapar™ will be much lower (estimated to be 3-5 fold by the sponsor, given the difference in metabolic ratios).

However, the overall safety from higher exposures at steady state (5-6 fold higher) with suprathreshold doses of 10 mg Zelapar (from tyramine challenge study, QTc study) should be evaluated by the Medical Officer."

I agree that it seems reasonable to conduct/complete the renal and hepatic impairment studies with Zydys selegiline as a phase 4 commitment. The following major reasons support this view :

- 1) increased exposure from Zydys selegiline (and its metabolites) via buccal absorption associated with renal or hepatic functional impairment would be expected to be considerably less than exposures from swallowed selegiline (i.e. Eldepryl);
- 2) the publication raising concerns about renal and hepatic impairment contains puzzling results that do not clearly seem scientifically sound mainly because of the inability to correlate increased exposure directly with increased impairment;
- 3) the reproducibility of the results of the publication seems unlikely likely;
- 4) the safety experience observed in short term PK studies of a high dose (10 mg/d) of Zydys selegiline in healthy volunteers and a longer term controlled study (# 8) of patients with Parkinson's Disease did not exhibit a substantially, or

markedly different safety profile for Zydys selegiline than exposure to lower doses (e.g. ≤ 2.5 mg daily);

5) the label can be adequately crafted to deal with the potential safety implications of increased selegiline exposure associated with renal or hepatic functional impairment.

I would particularly also like to note that the most recently conducted tyramine sensitivity study did not suggest a significant risk for hypertensive responses with significant oral tyramine exposure when Zydys selegiline exposure is increased up to 4 fold over the recommended daily dose (2.5 mg/d). Neither did the "thorough" QTc study suggest a clear indication of QTc prolongation with a similarly increased exposure (e.g. 4 fold increase with 10 mg/d). Nevertheless, this study was not able to exclude a possible 10 msec increase in QTc prolongation with the 10 mg daily dose when confidence intervals were analyzed. Thus, if patients were to be exposed to very high selegiline exposures (e.g. greater than the 4 fold increased exposures expected with 10 mg daily), it is difficult to comment on the nature and severity of safety issues that might arise or be experienced.

3.6.4 Clinical Reviewer Conclusions

- **I think that it is reasonable to determine the separate effect of renal and hepatic impairment on Zydys selegiline as a phase 4, post-approval commitment for the reasons outlined above here.**
- **I think that it is extremely important that a conservative approach be taken and that careful attention be given to the language in the label about describing the potential safety risks of increased selegiline exposure for patients who may have any degree of renal or hepatic functional impairment.**

Important elements of this description should note that :

- publication raised potential concerns about this issue;
- the publication did not suggest any direct correlation between increased selegiline exposure risk and severity of renal or hepatic functional impairment;
- exercising caution in all patients with any degree of renal and hepatic impairment, especially patients with indices of functional hepatic impairment such as decreased serum albumin OR increased prothrombin time OR increased serum bilirubin);
- from a practical perspective, caution can mean considering discontinuing Zydys selegiline if a patient with any degree of renal or hepatic impairment if a patient seems to be experiencing adverse reactions in greater number, frequency, or severity than might ordinarily be expected.

3.7 FDA Comment 3 – Food Effects on Selegiline Pharmacokinetics (Letter Page 3)

“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”.

3.7.1 Sponsor’s Conclusion

“In summary, based upon the evidence stated above, we believe that the Barrett study actually corroborates our study when the studies are examined more closely and comparisons include only examination of the morning dose. The discrepancy noted is due to comparing different doses, dosing regimens and differing meal compositions.”

3.7.2 Clinical Pharmacology Reviewer Summary Comments and Conclusion

“Overall conclusion from ISSUE 6:

The sponsor has made their best attempt to explain the differences in food effect from that observed in their study versus what was known of oral selegiline. In the Barret study oral selegiline was administered BID given 4 hours apart instead of a single dose in the sponsor’ study. The sponsor bases their argument on the profile observed at the initial 4 hours (first dose) and shows that the Cmax under fed condition is 83% that of the fasted arm. However, during these 4 hours the AUC(fed) is still 40% higher than AUC(fasted). After the second dose the AUC is 74% higher under fed conditions. The Cmaxs are slightly lower after both the doses in the Barret study however, the overall exposure is still higher. The sponsor speculated this to be due to the “Clinical lunch”, the contents of which are unknown and is speculated to somehow be inhibiting the metabolism of selegiline.

Given the limited knowledge of the complete data, the reason for the discrepancy is still not clear, however the sponsor has fulfilled their obligation of trying to explain the reasons that may lead to this difference.”

3.7.3 Clinical Reviewer Conclusions

- I concur with the Clinical Pharmacology reviewer that the reason(s) for the discrepancy between the sponsor's results/conclusion of a food effect and the opposite conclusion described in the swallowed selegiline (i.e. Eldepryl) label is still not clear. Nevertheless, I agree that the sponsor has fulfilled its obligation of trying to explain the reasons that may lead to this difference and discrepant conclusions.
- Considering that the reason for the discrepancy between the sponsor's findings and the results described in the Eldepryl still remain unclear, ~~_____~~
~~_____~~

b(5)

3.8 FDA Comment 5 – Safety Update (Letter Page 5)

“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.”*

3.8.1 Sponsor's Conclusion

“As there are no additional clinical studies performed since the last safety update submitted in our previous March 29, 2005 complete response submission, there are no new safety tables. However, we have included the following new safety information:

- World-wide experience with Zelapar obtained from Elan Pharmaceuticals, Inc.
- Updated Summaries of Product Characteristics (SPCs) from Europe
New literature search (January –Oct 2005), including strategy and listing of cited references”

3.8.2 Clinical Reviewer Conclusion

- Relatively little new safety information was submitted and my impression of the safety profile for Zydis selegiline remains unchanged from my previous reviews.

4 LABELING COMMENTS

I have provided my recommended comments/edits for the label using the last approvable letter label as the base document and showing my comments/edits as tracked changes.

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17 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

✓ Draft Labeling (b5)

✓ Deliberative Process (b5)

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

/s/

Leonard Kapcala
6/12/2006 11:32:27 AM
MEDICAL OFFICER

John, Here is my review of the response to
approvable letter. Please let me know if any
questions. Thanx. Len

John Feeney
6/13/2006 06:27:08 PM
MEDICAL OFFICER
See my cover memo

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MEMORANDUM

NDA 21-479 Zelapar (selegiline orally disintegrating tablets)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Response to Approvable Letter for Adjunctive Treatment for the
Management of Parkinson's Disease

DATE: September 30, 2005

The previous sponsor of this application, Elan Pharmaceuticals, was sent an Approvable Letter on February 7, 2003. In that letter, DNDP requested that the sponsor:

1. repeat a tyramine challenge study;
2. collect orthostatic BP data timed to dosing;
3. collect ECG data timed to dosing;
4. present adequate information on the metabolism of selegiline, either through in vitro studies or literature review;
5. present adequate information on the potential of selegiline to inhibit/induce hepatic enzymes (again through in vitro studies or literature review);
6. evaluate the need for additional drug-drug interaction studies based on #4 and #5 above;
7. clarify various issues, to include urinary excretion, food effect, and gender effect;
8. as phase 4 commitments, conduct PK studies with hepatic impairment and renal impairment;
9. as a phase 4 commitment, conduct a battery of reproductive and developmental toxicology and genotoxicity studies.

According to the draft labeling that accompanied the Approvable Letter, **carcinogenicity studies were "ongoing" at that time (2003).**

The new sponsor of this NDA, Valeant Pharmaceuticals, submitted a response to the Approvable Letter on December 15, 2004. That response was not considered a complete response by DNDP primarily because of problems with formatting. The sponsor submitted a new response on March 30, 2005 that DNDP considered a complete response.

Current reviews of the application include the clinical review, performed by Dr. Len Kapcala, and 3 separate biopharm reviews, all written by Dr. Andre Jackson.

As discussed in Dr. Kapcala's primary clinical review, the sponsor has adequately addressed the requests for a tyramine challenge study, BP data, and ECG data. Although the metabolism data presented is less than optimal, it is probably also adequate to support approval at this time.

The sponsor has also committed to perform (phase 4) the requested pharm/tox studies, a hepatic impairment study, and a renal impairment study.

Given this compliance with DNDP's requests, an Approval action would seem warranted at this time. However, in January 2005, Anttila et al (Clin Pharmacol Ther 2005;77:54-62) published the results of a study in 10 patients with impaired liver function and 10 patients with impaired kidney function which suggest extreme increases in selegiline exposure in such patients after dosing with oral selegiline. Unfortunately, the published report does not adequately characterize the stages of hepatic and renal impairment studied. With the availability of this new (but very limited) data, it would be impossible to write product labeling for Zelapar that could adequately inform the prescriber of the risks of Zelapar in what will undoubtedly be primarily an elderly patient population with frequent co-morbidities. Now a phase 4 commitment to perform hepatic and renal impairment studies no longer seems sufficient; these studies will be needed pre-approval to better characterize these findings and allow for the safe use of Zelapar.

To delay approval of Zelapar may seem contradictory while oral selegiline continues to be marketed. The AUCs of selegiline after oral selegiline and Zelapar (at the to-be-marketed dose) are comparable and the Cmax with Zelapar is only two-fold higher. However, given the one (limited) report of extreme increases in exposure in hepatically- and renally-impaired subjects, it seems imprudent to take any regulatory action that would encourage increased use of selegiline until this signal is better characterized.

In recent months, Dr. Kapcala discussed the Anttila study with the sponsor. The sponsor proposed that a warning be included in labeling stating that care should be exercised when administering Zelapar to patients with hepatic and/or renal impairment.

At the same time, the sponsor correctly pointed out that the degree of hepatic or renal impairment could not be assessed from the Anttila publication. The problem that arises from that fact is that informed labeling cannot be written unless the population at risk is identified. There is some information in the Anttila article to suggest that even mild hepatic or renal impairment might predispose to the large increases in systemic exposure. Therefore, the sponsor should characterize the population at risk pre-approval.

In the rest of this memorandum, I will comment briefly on the new tyramine challenge study and the ECG data timed-to-dosing.

Tyramine Challenge Study 101

The new study was a randomized, double-blind, double-dummy, parallel group study. Subjects, n=80, were randomized to 5 treatment groups:

- Zelapar 1.5mg
- Zelapar 5mg
- Zelapar 10mg
- Placebo
- Phenelzine (active control)

Subjects were dosed as above over 16 days, with tyramine challenges of 12.5mg, 25mg, 50mg, 100mg, 200mg, and 400mg performed on the mornings of days 11-16.

During baseline days -5 through -1, subjects were challenged with tyramine at doses of 25mg, 50mg, 100mg, 200mg, and 400mg. Only subjects who had 3 consecutive BP elevations \geq 15mmHg in response to one of these doses were then randomized.

Both pre- and post-randomization, dose escalation of tyramine stopped if an individual met one of the pre-specified safety criteria.

For the highest matched (pre- and post-randomization) tyramine dose achieved for any individual, the primary outcome was the difference between the highest systolic BP elevation experienced pre- and post-randomization. For example, if an individual received a maximum tyramine dose of 200mg during baseline and a maximum tyramine dose of 100mg post-randomization, the greatest change in SBP after 100mg tyramine was compared from post-randomization to baseline.

The analysis of this outcome showed essentially no difference between the Zelapar groups and placebo for all tyramine doses \leq 100mg. (A high-tyramine meal is usually considered to contain about 50-75mg tyramine.) The positive control was shown to increase sensitivity to tyramine.

A secondary outcome was a comparison of threshold dose ratios (TDRs), a more traditional analysis. For this approach, the tyramine dose required to achieve a certain threshold BP increase (usually on the order of a 30mmHg rise in SBP) at baseline is compared to the tyramine dose required in the presence of the study drug. If tyramine 400mg is required at baseline and tyramine 50mg is required on study drug, the TDR would be 8.

Interestingly, the ordering of the TDRs for the 3 Zelapar dose groups results in a reverse dose-response relationship. Dr. Kapcala notes in his discussion that this results from considerable variability in the identification of the threshold dose for individual subjects and the impact of a few subjects with spurious results on the

mean values. In fact, a number of subjects experienced an inverse threshold dose ratio. Dr. Kapcala created a Table 32 in his review showing the numbers of subjects meeting the BP threshold at given tyramine doses during the study. I note from his table that, during baseline, 8 subjects met a threshold of at least one 30mmHg SBP increment at tyramine doses of 100mg or less. During baseline, 4 subjects met a threshold of two successive 30mmHg SBP increments at a tyramine dose of 100mg. This reinforces the need for a placebo group in tyramine challenge studies.

The highest TDR for a Zelapar dose group is 2.33 for Zelapar 2.5mg. This is just slightly greater than the TDR for the placebo group and less than the TDR of 7 for the positive control.

Of additional note, in the Approvable Letter, DNDP had asked the sponsor to address the timecourse of tyramine sensitivity after Zelapar dosing. In the biopharm review, Dr. Jackson has analyzed trough selegiline levels at days 8-10 of dosing and concluded that steady state selegiline levels are in fact achieved after 2 weeks. Therefore, the new tyramine challenge data would seem to adequately address the steady state effect.

Dr. Kapcala points out 2 negative aspects of the provided study. First, doses of tyramine greater than 400mg were not provided to better characterize the dose-response. Second, oral selegiline at the recommended dose of 5mg bid was not included as a comparator arm in the study. I would agree with both these points.

QT Study

To address the division's request for ECG data timed to dosing, the sponsor performed a new study in healthy volunteers. Dr. Kapcala has reviewed that study in detail in his review. In that study, 160 subjects were randomized to 4 treatment groups: placebo, Zelapar 2.5mg/day, Zelapar 10mg/day, and moxifloxacin 400mg. The active Zelapar subjects and the placebo subjects were treated for 10 days. The active control subjects received Zelapar placebo tablets for 9 days followed by one 400mg moxifloxacin tablet on the 10th dosing day.

QT interval was corrected for rate for each subject using **the subject's baseline** ECGs to examine the relationship of RR and QT. The mean QTci change from baseline was determined at multiple timepoints after dosing on day 10 and compared across groups. The moxifloxacin group showed a 5-8 msec change from baseline between hours 2-5 and again at hour 18. Curiously, the Zelapar 2.5mg group also showed a 6 msec increase from baseline at hour 18 and the Zelapar 10mg group showed a 3 msec increase at hour 18. Otherwise both Zelapar groups tended to show a negative change from baseline at all other timepoints after dosing. The placebo group also tended to show small negative changes from baseline at all timepoints, with a 3msec increase at hour 18.

Dr. Kapcala's review provides tables showing the results for the 2 Zelapar groups at all timepoints, showing the difference from placebo with the 95% confidence intervals. There is a 5msec difference between Zelapar 10mg and placebo at 12 hours (CI: -2.6,12.3). The difference between Zelapar 2.5mg and placebo at the same timepoint is 3msec (CI: -4.4,10.6). At the same timepoint, the difference between moxifloxacin and placebo is 7.7msec.

Of interest, the results for the Zelapar groups at 12 hours are driven entirely by the results for female subjects, with female subjects showing a 10msec Zelapar10mg/placebo difference at 12 hours.

There is no obvious pharmacokinetic explanation for either the 12 hour finding or the gender difference. Of note, there is also a gender difference at 3 hours, but in the other direction (a 5msec difference between Zelapar 10mg and placebo for males, but only a 1.4msec difference for females). This might suggest that the gender differences observed at some points only reflect the overall variability of the data. Given what is known about Tmax for selegiline and its metabolites, the 12 hour finding is surprising; given the multiple timepoints examined, again the question arises whether the 12 hour result represents nothing more than the overall variability of the data. In support of this notion, the active-control moxifloxacin group shows the same gender effect at 12 hours, an unexpected finding.

There were no subjects with QT intervals > 500msec and no subjects with changes from baseline > 60msec. PK/PD modeling within the Zelapar dose groups suggested a negative slope for the concentration/QT prolongation relationship.

Metabolism

There is conflicting data on the CYP450 enzymes involved in the metabolism of selegiline. Roles for CYP2B6, 2C19, 3A4, and 1A2 are suggested by various studies. One clinical study, using itraconazole as the 3A4 inhibitor, suggested no change in selegiline metabolism. Another clinical study examining various polymorphisms of 2C19 suggested no difference in exposure to selegiline based on 2C19 expression.

One literature report, reviewed by Dr. Jackson, suggested that at least some sex steroids may inhibit the metabolism of selegiline, resulting in significant increases in exposure.

While the sponsor has reviewed some of this literature, new studies to address some of the conflicting data have not been done.

Conclusions/Recommendations

The sponsor should be sent another Approvable Letter requesting that studies in renal and hepatic impaired patients be conducted pre-approval. Given the conflicting data on metabolism, the sponsor should be asked to perform further studies to clarify which CYP450 enzymes are involved in the metabolism of selegiline. Appropriate drug-drug interaction studies should be done, based on the above results. Because there is already a report of sex steroids resulting in excessive exposure to selegiline, appropriate follow-up interaction studies of this combination should be performed.

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this page is the manifestation of the electronic signature.**

/s/

John Feeney
10/24/2005 10:38:37 AM
MEDICAL OFFICER

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MEMORANDUM

DATE: September 29, 2005

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-479

SUBJECT: Action Memo for NDA 21-479, for the use of Zelapar (selegiline) 1.25 mg Tablets

NDA 21-479, for the use of Zelapar (selegiline) 1.25 mg Tablets in the treatment of patients with Parkinson's Disease, was submitted by Elan Pharmaceuticals, Inc., on 3/29/02. Selegiline, an MAO-B inhibitor, is currently marketed as Eldepryl for the same indication, and Elan's application was submitted under 505(b)(2) of the FD&C Act. The division issued an Approvable letter on 2/7/03. In that letter, the division expressed the following concerns and requests for additional data:

Tyramine challenge studies

For numerous reasons, the division did not agree with the sponsor's conclusions that a therapeutic dose of selegiline (2.5 mg given once a day) could be given safely in the face of a tyramine-rich meal. Therefore, we asked the sponsor to perform a new tyramine-challenge study.

Statistical concerns

We asked the sponsor to address what appeared to be analysis-dependent outcomes in Study 25.

Blood pressure concerns

We had concluded that the sponsor had not adequately documented Zelapar's effect on blood pressure, especially timed to dosing (the C_{max} of Zelapar is higher than that achieved after an equivalent dose of Eldepryl). We asked the sponsor to incorporate appropriate blood pressure monitoring in the requested tyramine-challenge test.

Potential QT prolongation

We noted that the sponsor had presented conflicting information on Zelapar's effects on the QT interval. For this reason, we asked them to further characterize Zelapar's effect, if any, on the QT interval. We believed that this data could be collected during the tyramine-challenge study.

CMC

We requested that the sponsor address numerous CMC questions.

Clinical Pharmacology

We asked the sponsor to address numerous questions:

- 1) Because literature reports presented conflicting information on the metabolism of selegiline, we asked the sponsor to adequately characterize the CYP450 enzymes necessary for the metabolism of selegiline. We acknowledged that this information could be obtained from the literature, if appropriate. If adequate data did not exist in the literature, we requested that they perform additional in vitro studies.
- 2) We further asked the sponsor to provide information on selegiline's potential to induce and/or inhibit metabolizing enzymes. Again, this information could have been obtained from the literature, or from their own studies.
- 3) We informed the sponsor that, depending upon the responses to the first 2 questions, drug interactions studies may need to be performed.
- 4) We asked for clarification about the urinary excretion of selegiline and its metabolites.
- 5) We asked for additional clarification of conflicting information about the effect of food on the absorption of selegiline.
- 6) We asked for additional analyses of the effect of sex on selegiline metabolism.

Phase 4 commitments

We asked the sponsor to commit to performing the following Phase 4 studies:

- 1) Conduct a pharmacokinetic (PK) study in patients with hepatic impairment
- 2) Conduct a PK study in patients with renal impairment
- 3) Conduct a complete battery of reproductive and developmental toxicology and genotoxicity studies

After our Approvable letter issued, Elan Pharmaceuticals, Inc., sold the drug to Valeant Pharmaceuticals. The new sponsor responded to the Approvable letter in a submission dated 3/29/05. This submission has been reviewed by Dr. Len Kapcala, medical officer, Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics, Dr. David Claffey, chemist, and Dr. John Feeney, neurology team leader. The review team recommends that the sponsor be issued a second Approvable letter. I will briefly present the relevant data, and the rationale for the division's action.

Tyramine-challenge

The sponsor has performed a new tyramine-challenge study, utilizing Zelapar doses of 1.25 mg, 2.5 mg and 10 mg, placebo, and Phenezine (active control). Patients were dosed with Zelapar for 16 days, sufficient to reach steady state. Although the study did not incorporate all of the design elements we had requested (for example, the sponsor did not include an Eldepryl arm, and the maximum dose of tyramine used was 400 mg), Dr. Kapcala concludes that there is no clinically meaningful effect on blood pressure in the face of an adequate tyramine challenge (one that exposed patients to an amount of tyramine considerably greater than that included in a tyramine-rich meal) in patients treated with Zelapar at doses up to 10 mg.

Statistical Concerns

The statistical concerns, though never critical, have been resolved.

Blood pressure analyses

The sponsor has now presented adequate data on Zelapar's effects on blood pressure, derived from the tyramine challenge study. Dr. Kapcala concludes that there were no significant effects of these doses on either resting or orthostatic blood pressure.

QT Effects

The sponsor has performed a dedicated study to examine the effects of Zelapar on the QT interval.

This was a randomized, double blind trial in which 40 patients/group (20 men and 20 women) were randomized to the following treatments for 10 days:

- 1) Zelapar 2.5 mg/day
- 2) Zelapar 10 mg/day
- 3) Moxifloxacin 400 mg (single dose on Day 10 of dosing; placebo prior)

Continuous EKG was recorded at baseline and on the last day of dosing. Triplicate QT interval data obtained at each time point (hours 1, 2, 3, 4, 5, 6, 8, 12, and 18.5 hours after dosing) were used to assess the drug's effect on the QT interval. Dr. Kapcala describes the details of the design and conduct of the study in his review.

In actuality, 44 subjects were enrolled in each group, save for the Zelapar 10 mg group, in which 45 subjects were enrolled (total N=177; 165 subjects completed the study).

Although multiple QT correction factors were computed, I will present the results for the QTcI, based on individual patient data (the results of the other analyses mirror the individual analyses).

According to ICH Guideline E14, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs:

The threshold level of regulatory concern, discussed further below, is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms.

The document provides further clarification:

...a negative 'thorough QT/QTc study' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms. This definition is chosen to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval is not greater than around 5 ms. When the largest time-matched difference exceeds the threshold, the study is termed 'positive'. A positive study influences the evaluations carried out during the later stages of drug development, but does not imply that the drug is pro-arrhythmic.

Neither dose of Zelapar demonstrated a prolongation of the mean QTc interval compared to placebo, but there was the expected mean increase of about 5 msec (actual value 4.73 msec) compared to placebo in the moxifloxacin group, validating the sensitivity of the assay. Additionally, outlier analyses did not demonstrate any differences between Zelapar and placebo, while there were increases seen with moxifloxacin. However, the following table displays the analyses of the data at each time point around the maximum time-matched mean comparisons, as well as at the times at which the upper bound of the one-sided 95% confidence interval includes 10 (the table also includes additional time points of interest, which will be discussed below):

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Drug	Time from Dosing (Hours)	Mean Difference From placebo (msec)	Upperbound
Zel 2.5 mg	3	1.4	7.4
	4	2.9	NC*
	12	3.1	8.4
	18	3.1	NC
	23.5	2.6	NC
Zel 10 mg	3	3.2	9.0
	4	-0.5	NC
	12	4.9	10.1
	18	0.3	NC
	23.5	0.2	NC
Moxifloxacin	3	12.6	NC
	12	7.5	NC

*NC-Not Calculated

Dr. Kapcala further presents the results by sex:

Males

Drug	Time from Dosing (Hours)	Mean Difference From placebo (msec)	Upperbound
Zel 2.5 mg	3	0.4	8.9
	4	-1.4	NC
	12	-1.3	6.3
	18	2.9	NC
	23.5	7.2	NC
Zel 10 mg	3	5.0	13.0
	4	-4.0	NC
	12	-0.5	6.9
	18	0.5	NC
	23.5	4.0	NC
Moxifloxacin	3	11.6	20.2
	12	-1.0	6.6

Females

Drug	Time from Dosing (Hours)	Mean Difference From placebo (msec)	Upperbound
Zel 2.5 mg	3	2.2	10.9
	4	6.4	NC
	12	7.5	14.8
	18	3.3	NC
	23.5	-1.6	NC
Zel 10 mg	3	1.4	10.0
	4	3.0	NC
	12	10.2	17.5
	18	0.1	NC
	23.5	-3.5	NC
Moxifloxacin	3	13.3	21.9
	12	15.7	23.1

CMC

The CMC issues have been resolved.

Clinical Pharmacology

Metabolism

As described by Dr. Jackson, the sponsor submitted several literature reports that they presumably believe adequately document the CYP450 enzymes responsible for the metabolism of selegiline.

The authors of one article (Taavitsainen et al, Pharmacology and Toxicology, 2000) examined selegiline metabolism in human liver microsomes. In this study, they also examined the effects of specific 1A2, 2C9, and 2C19 inhibitors on selegiline metabolism. These authors concluded that CYP 1A2 and 3A4 are involved in selegiline metabolism.

The authors of another article (Hidestrand et al, Drug Metabolism and Disposition, 2001) examined the metabolism of selegiline in yeast cells encoded with human CYP450 enzymes 1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and

3A4. These authors concluded that CYP2C19 and 2B6 are involved in the metabolism of selegiline.

A third article (Laine et al, European Journal of Clinical Pharmacology, 2001), describes the PK of selegiline in 6 extensive (EMs) and 6 poor (PMs) 2C19 metabolizers. As described by Dr. Jackson, mean AUC of selegiline was about 60% greater in PMs compared to EMs, and desmethylselegiline levels were about 70% greater in PMs compared to EMs. The authors conclude, based on these small differences, that 2C19 is not an important metabolizing enzyme of selegiline.

A fourth article (Kivisto et al, European Journal of Clinical Pharmacology, 2001) describes a study in 12 healthy young adults given a single dose of selegiline and itraconazole (200 mg/day for 4 days; maximum recommended dose is 400 mg/day), a potent inhibitor of CYP3A4. The authors conclude that there were no significant effects on selegiline levels.

Several additional drug interaction studies were identified by the review team. Specifically, these studies examined the interactions of selegiline with sex steroids.

Laine et al (British Journal of Clinical Pharmacology, 1999) studied 8 young adult women who received a single dose of Eldepryl (either 5, 10 mg, 20 mg, or 40 mg) in a 4 period cross-over study. Four of the women were receiving oral contraceptives, and 4 were not. The AUC of selegiline in the women receiving oral contraceptives ranged from 16-45 times greater than that in the women not being treated with contraceptives (the largest increase was seen in the low dose selegiline group). Desmethylselegiline levels were not materially different between the two groups.

Recent work suggests that some sex steroids are inhibitors of CYP3A4.

Another article (Palovaara et al, European Journal of Clinical Pharmacology, 2002) examined the interaction of selegiline and hormone replacement therapy (HRT containing estradiol and levonorgestrel) in 12 young adult women. In this cross-over study, women received either HRT or placebo for 10 days. On Day 10 of each period, subjects received a single 10 mg dose of selegiline. There were minimal changes in the PK of a single dose of selegiline in the face of HRT treatment.

Although, as noted above, we had asked the sponsor to commit to perform studies in patients with renal and hepatic disease in Phase 4, the review team has become aware of a very recent literature report in patients with these conditions.

In this study (Antilla et al, Clinical Pharmacology and Therapeutics, 2005), the PK of selegiline was examined in 10 patients in each of four groups: normals, liver disease (described as having a diagnosis of liver dysfunction that had been confirmed histologically), drug induced liver function (patients receiving anticonvulsant drugs, known to be inducers of metabolizing enzymes), and kidney disease group (patients with stable long-term renal disease).

The following table presents the mean baseline values of relevant laboratory tests for the liver and renal impaired patients:

Lab Test	Hepatic Impaired	Renal Impaired
AST	46.4	27.6
ALT	64.1	33.6
Alk Phos	253	172
GGT	254	36.1
PIIINP	5.47	4.10
Urea	5.67	12.2
Creatinine	79.6	173

Normal ranges:

AST	10-35
ALT	10-35
Alk Phos	50-200
GGT	5-50
PIIINP	1.7-4.2
Urea	1.7-8.3
Creatinine	55-115

Patients were given a single 20 mg dose of selegiline.

The C_{max} of selegiline increased by about 7 fold in the hepatic impaired patients, and by about 4 fold in the renally impaired patients. The AUC of selegiline increased by about 17 fold in the hepatic impaired patients, and by about 5-6 fold in the renally impaired patients.

In the induced patients, the C_{max} decreased to about 1/15 of the control level, and the AUC was decreased to about 1/24 the control level.

We had also asked the sponsor to address the apparently qualitative differences in absorption between Eldepryl and Zelapar when given with food; they have not done so.

In addition, according to Dr. Jackson, the sponsor has adequately documented that selegiline is unlikely to inhibit metabolizing enzymes, but they have not determined if it has the capacity to induce these enzymes.

COMMENTS

The sponsor has responded to most of our requests for additional information. In particular, they have performed adequate tyramine-challenge and thorough QT studies, and have further documented the effects of Zelapar on resting and orthostatic blood pressure. In addition, they have provided literature reports that they believe adequately address our questions about the metabolism of selegiline.

I agree with Dr. Kapcala that the sponsor has demonstrated that, at Zelapar doses up to 10 mg/day, there is no appreciable hypertensive response to an adequate test dose of tyramine. All other things being equal, therefore, if we were to approve the application at this time, we would be able to do so without dietary restrictions being imposed.

The interpretation of the thorough QT study is somewhat more problematic. Dr. Kapcala believes that the study should be considered a "positive" study according to the ICH guideline quoted earlier, because at the time(s) of the maximum drug-placebo difference in the means for the QTcI interval, the one-sided 95% confidence interval (CI) includes 10; he concludes that this is true for hours 3 and 12 post-dosing (it is worth noting that the T_{max} for selegiline is about 30 minutes). He does conclude that the particular pattern of findings is not easily understandable, but he does argue that there appears to be a suggestion of a dose response for QT prolongation, based on the results of his analyses of the 95% confidence interval approach. He acknowledges that the usual analytic approaches used to assess QT prolongation are negative (mean between-treatment changes from baseline and outlier analyses) for both doses of Zelapar, while these traditional analyses (as well as the confidence interval approach) detect the expected effect of the active control moxifloxacin.

Examining the analyses of all patients (men and women together), there appears to be no CI signal at any time after dosing for the 2.5 mg dose (it is also worth noting that the maximum between-treatment mean difference occurs at 12 and 18 hours, and that the 4 hour time comparison is greater than the 3 hour comparison, as is the 23.5 hour comparison). In short, there is no finding of interest at the low dose. At the high dose, the CI includes 10 only at the 12 hour comparison; although the upper bound of the CI at 3 hours is 9. The upper bound of the CI includes 10 for essentially all time points for moxifloxacin.

Examination of the data in males reveals the largest between-treatment mean at 23.5 hours (7.5 msec) in the low dose. Interestingly, the upper bound of the CI at 3 hours is 8.9, close to 10, while the mean difference at that time is 0.4 msec. At

the high dose in males, the largest mean difference is at 3 hours (5 msec), with an upper bound of the CI of 13. The next highest mean difference (4 msec) is at 23.5 hours. No other difference at any other time is close to important. For moxifloxacin, the largest mean difference is at 3 hours (11.6), with an upper bound of the CI of 20.2.

In women, at the low dose, the largest mean difference is at 12 hours (7.5) with an upper bound of 14.8, but the mean difference at 4 hours is also 6.4. At 23.5 hours, the mean difference is -1.6, very different from that seen in males at this dose. At the high Zelapar dose, the largest mean difference is at 12 hours (10.2) with an upper bound of 17.5. The upper bound of the CI at 3 hours is 10, but the mean difference at that time is 1.4 msec. At 23.5 hours, the mean difference is -3.5. For moxifloxacin, the mean differences are 13.3 at 3 hours and 15.7 at 12 hours, and the upper bounds of both CIs are over 20.

It is possible to read these results as being "positive" according to the ICH definition, utilizing the CI approach, but I believe the results are quite variable and certainly do not provide a consistent picture. The overall results present a picture of no finding (even by the ICH rule) for the low dose, and for the high dose, the upper bound of the CI is 10.1 only at 12 hours, at which point the highest mean difference is seen (4.9 msec). At the times at which the greatest mean differences were seen at the 2.5 mg dose (save for 12 hours), there are no findings in the 10 mg dose group. None of the differences approach those seen with the positive control moxifloxacin.

When the results are broken down by sex, there appear some interesting findings, but one can ask if it is appropriate to do so. As Dr. Kapcala notes, there is no appreciable difference in the PK between the sexes, and we are not aware of any expected sex-based PD differences (although, of course, there could be). Although the results are interesting to examine, they are best considered post hoc subgroups, the results of which should be considered highly preliminary (especially, again, given the considerations described above).

In males, the maximum mean difference is seen at 23.5 hours at the low dose (7.2), a difference that is considerably greater than that seen at any time point at the high dose. Moxifloxacin shows an 11.6 msec QT interval at 3 hours. At the high dose in men, the upperbound includes 10 at 3 hours only; in females, the upperbound at 3 hours also includes 10, but recall that the CI for the combined data **excludes** 10 at 3 hours, strongly suggesting that any finding in the individual sexes at 3 hours is spurious (importantly, perhaps, the 3 hour finding at the high dose is the only time point at which there is consistency in both sexes in reaching the ICH CI standard for any Zelapar dose).

The only potentially consistent finding for Zelapar that could even suggest, in my view, that there is a dose response for QT prolongation is in women, where the largest mean difference is at 12 hours (the finding at 3 hours is inconsistent,

although the CIs include 10 at both doses; however, the mean difference [and the upperbound of the CI] is greater in the low dose than in the high dose, and, in any event, by the ICH "rule", we should be examining the time point of the maximum difference, which is at 12 hours in both doses). However, again, there is no a priori reason to expect that the maximum difference would be seen at this time, (given the PK of the parent and metabolites), given the completely opposite findings in men (the smallest differences are seen at 12 hours in men), and given the inexplicable finding that the greatest differences seen with the positive control, moxifloxacin, are also seen in women at 12 hours.

Although, as I noted, it is possible to consider this a signal for QT prolongation with Zelapar, it is at least clear to me that there is no such signal at the low (i.e., therapeutic) dose. Further, even at the high dose, it is clear that, even if there is a "signal", it is clearly less than that seen with the positive control (although I take Dr. Kapcala's point that the 5-6 msec prolongation expected with moxifloxacin was likely derived as an average prolongation without reference to the specific time course; indeed, the average prolongation with moxifloxacin in this study was about 5 msec, but the detailed examination of the time course presents interesting data that might require some additional thought). Finally, given what I believe to be significant inconsistencies in the data (especially at the high dose), I would not require any additional work on Zelapar's effect on the QT interval, all things being equal.

Turning to the metabolism of selegiline, the picture is not entirely clear.

Different authors have identified different metabolizing enzymes. One group has identified CYP 1A2 and 3A4 as important, while another group has identified 2B6 and 2C19 as important. The first study did not examine CYP2B6 as a potential metabolizing enzyme, but it did examine 2C19 and did not find it to be important in selegiline metabolism. The second study did examine 1A2 and 3A4, and did not find them to be important in selegiline metabolism. An in vivo study suggests that inhibition of 3A4 does not produce important increases in selegiline plasma levels, and another group found, based on genetic polymorphism, that 2C19 status is not very important. These findings taken together are hard to reconcile; the in vivo studies might suggest that multiple enzymes may be responsible (to varying degrees) in selegiline metabolism, and that inhibiting (at least) some of them individually is not clinically important.

In addition, several small studies have examined the effects of concomitant HRT or OCs on selegiline metabolism. The study of HRT showed no important effect on selegiline metabolism, but in the OC study, selegiline levels were elevated up to 40 fold in women taking OCs. Another article suggests that sex steroids (in particular, those used in the OC study) can have important 3A4 inhibiting effects. These findings at least suggest that, indeed, inhibition of 3A4 can have profound effects on selegiline levels, but, again, this conclusion would directly contradict the results of the itraconazole study.

Particularly disturbing are the results of a small study in which patients with liver or renal disease experienced significant elevations of selegiline levels. Unfortunately, the article describing this study does not provide sufficient details to permit a complete understanding of the results.

In particular, it appears that the degree of hepatic or renal disease was relatively mild (at least judged by the mean laboratory abnormalities; oddly, though, despite the apparent mild disease, the article states that the liver disease was "histologically confirmed" in all patients), but the elevations of selegiline levels were quite high (up to 17 fold in the hepatic patients and 6 fold in the renal patients). According to the paper, at least for the hepatic patients, 4 of the 10 seemed to have the greatest degree of increased selegiline levels, but the authors state that there was no correlation between degree of disease and selegiline levels.

Interestingly, in this study there were profound effects on selegiline levels in patients receiving inducing AEDs. We do not know which AEDs were given concomitantly, so it is impossible to know which enzymes were induced. Many AEDs are known to induce CYP3A4; if this was true in this study, this would be evidence that 3A4 is at least involved in selegiline metabolism (though this finding would not necessarily imply that 3A4 is a particularly important metabolizing enzyme).

It is clear that the literature provides, at the best, a very unclear picture of the enzymes involved in the metabolism of selegiline, and, at the worst, contradictory information. Is this fatal to the application?

Clearly, selegiline has been a marketed drug in this country for a considerable duration, almost 20 years and, just as clearly, it has been marketed in the absence of complete information on its metabolism. Although this is obviously not ideal, we are not aware of any major adverse health consequences of this lack of information. In particular, we are not aware of any drug-drug interactions of a PK nature that expose patients to a significant risk.

However, it is possible that such interactions are occurring and escaping our attention. It is first possible, of course, that such interactions are occurring, causing considerable increases in selegiline levels, but that these increased levels have no important clinical consequences. However, in my view, the absence of reported serious adverse events in selegiline users cannot be taken as reliable evidence either that these interactions are not occurring, or that they are occurring without clinical consequences. Specifically, we have no experience with the markedly elevated selegiline levels that some of the data suggest may occur as the result of certain interactions. At these higher levels, we can at least expect that selegiline would lose its specificity for MAO-B inhibition, giving rise to tyramine sensitivity. Were this to happen, with resulting hypertensive

crises/strokes in patients ingesting a high tyramine meal, it is quite likely that these events would not be reported as post-marketing adverse events, because such events are common in the population for whom selegiline is approved, and in whom it is most commonly used. Given this fact, and the probably quite low level of suspicion that such an event could be drug (interaction) related, it is reasonable to assume, in my view, that very few such events would be reported. Similarly, it is possible that such high levels might result in other adverse events considered common in the elderly population of selegiline users. For example, if one were to read the results of the QT study to suggest a potential effect of the 10 mg Zelapar dose on the QT interval (although as I have noted above, I do not believe that this can be considered a real finding at this point), one could imagine that the considerably higher levels that might be generated as a result of a particular interaction might be associated with a real risk of a fatal arrhythmia, again an outcome not likely to be reported as a drug related event in this population. Even if the QT study is not read this way, it is possible that the presumed elevated levels could result in QT prolongation.

In short, the possibility that, if drug-drug interactions with serious health consequences are occurring that they are not being prominently reported to the post-marketing adverse event database, is very real. The absence of such reports does not, in my view, reliably suggest that they are not occurring.

Even if they are occurring, it is perhaps at least theoretically possible to consider approving the drug with labeling that warns against using drugs that inhibit any of the CYP450 enzymes that are likely (based on the literature reports identified) to inhibit (or induce) selegiline metabolism. This, however, would be quite problematic, and would result in an extraordinarily large list of drugs that could not be given in concert with selegiline; such labeling would be largely unworkable in my view. One could, I suppose, presume, as I suggested earlier, that multiple enzymes are involved in selegiline metabolism, and that inhibiting only one at any given time might not result in significant selegiline levels. If this were the case, it is possible that labeling need not be so restrictive. However, we are not yet sure that this is true.

Beyond the possibility of significant drug-drug interactions based on enzyme inhibition (and induction), there is the disturbing finding that patients with hepatic or renal disease have markedly elevated plasma levels of selegiline. What is particularly disturbing is that, in the one article that describes this result, there seemed to be no correlation between severity of disease and selegiline levels. Although this is difficult to understand, this is what is described. The degree of pathology (at least as measured by enzyme elevation in the hepatic patients and urea and creatinine in the renal patients) appears quite mild (it is, I suppose, possible that patients with hepatic disease were profoundly impaired, to the point where LFT elevations are misleadingly low). In any event, we have no way of knowing, if these elevations in plasma selegiline levels are real, which patients would be at risk. For example, if we knew that only severely compromised

patients experienced marked selegiline level elevations, labeling could warn that the drug should ordinarily not be used in these patients. However, we do not have this information, and many elderly patients will have the degree of hepatic and/or renal disease described in the patients in this study. For this reason, and given the aforementioned concerns about the possibility of significant clinical consequences of markedly elevated selegiline plasma levels, it seems difficult, if not impossible, to write adequate labeling to protect the elderly population from these potential risks.

Although I have noted why I do not believe that the absence of reports of serious adverse events related to elevated selegiline plasma levels (if they occur) can be taken as reliable evidence that these events are not occurring, it is still fair to raise the question of whether or not the availability of selegiline currently makes it reasonable to approve Zelapar now, for reasons of equity.

One could argue that making Zelapar available now would not increase the risks to the population of patients with Parkinson's Disease above the risks they now face from Eldepryl.

It is true that the levels of selegiline derived from Zelapar are slightly greater than those achieved with the approved dose of Eldepryl, and therefore it could be argued that patients will be exposed to higher levels than is the case now. Further, because Zelapar may be easier to administer to some patients, there may be increased use overall of selegiline. These two factors could serve as an argument to prevent Zelapar's approval now. Although these arguments have some merit, I do not believe that they are compelling.

In my view, Zelapar should not be marketed at this time because it seems imprudent to approve the product with so much unknown about critical aspects of its use, regardless of the fact that Eldepryl is available and that our ignorance of these matters applies directly to it as well. Simply, this information is necessary given our perspective of what it is critical to know about the safe use of a product in 2005. The fact that another (essentially identical) product is currently available does not justify the approval of this new product in the absence of this critical data. This judgment, incidentally, is not a novel one. In our Approvable letter, we informed the sponsor that all of this data would be necessary for approval (although we permitted the sponsor to address these concerns with literature reports, we noted that if literature reports were not adequate, additional studies would need to be done). It is true that we stated in the Approvable letter that studies of patients with hepatic and renal disease could be performed after approval, but that was before we became aware of the study that strongly suggests that these impairments can have profound (and, again, potentially dangerous) effects on selegiline metabolism. It would be inappropriate, in my view, given these findings, to permit approval without more information on these critical points (that is, a full and adequate account of the enzymes responsible for selegiline metabolism, adequate in vivo interaction studies if necessary, and a

complete understanding of the effects on selegiline metabolism of varying degrees of hepatic and renal dysfunction). Depending upon the results of these studies, of course, it may be necessary for the sponsor to conduct additional safety examinations (possibly, for example, a through QT study and tyramine challenge studies at much higher doses).

For the reasons cited above, then, I will issue the attached Approvable letter with appended draft labeling.

Russell Katz, M.D.

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/s/

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CLINICAL REVIEW

Application Type 21479
Submission Number N000
Submission Code AZ

Letter Date 3/29/05
Stamp Date 3/20/05
PDUFA Goal Date 9/30/05

Reviewer Name Leonard P. Kapcala, M.D.
Review Completion Date 9/29/05

Established Name Zydis selegiline
(Proposed) Trade Name Zelapar
Therapeutic Class monoamine oxidase B inhibitor
Applicant Valeant Pharmaceuticals

Priority Designation S

Formulation Zydis (oral disintegrating tablet)
Dosing Regimen daily
Indication adjunctive treatment of patients
with Parkinson's disease who are
being treated with
levodopa/carbidopa and who
exhibit deterioration in the quality
of their response to this therapy

Intended Population advanced Parkinson's Disease

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1. EXECUTIVE SUMMARY

Background and Introduction

Conventional selegiline is currently approved (1989) in the U.S. as well as in several other countries for the treatment of patients with Parkinson's disease (PD) who are receiving levodopa/L-DOPA (LD) therapy (with or without a peripheral decarboxylase inhibitor) and who are experiencing deterioration in their therapeutic response to LD. Selegiline is thought to exert its therapeutic effect via inhibition of the monoamine oxidase (MAO) B enzyme and the decrease in dopamine metabolism and turnover. Selegiline is marketed in the U.S. as Eldepryl®, a formulation that is swallowed.

Zydis selegiline (ZS) is a rapidly-disintegrating oral dosage formulation of selegiline consisting of an open matrix of water-soluble ~~_____~~

This formulation disintegrates quickly (e.g. beginning within seconds) in saliva on the tongue, releasing selegiline into the saliva, and does not require added water to aid disintegration, dissolution or absorption. Major theoretical advantages of the ZS formulation include : 1) improved patient compliance with the easily administered tablet that rapidly dissolves on the tongue, especially for patients with swallowing difficulties; 2) reduced variability in absorption relative to orally-administered standard tablets, with potentially more predictable clinical effects; and 3) reduced overall exposure to selegiline and metabolites (based on administered dose), and reduced production of potentially active metabolites.

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The original IND (47005) for ZS was submitted to the FDA in 1994 by RP Scherer DDS. Eventually this product was sold to Elan Pharmaceuticals who submitted an NDA (21479) to the Agency on 4/8/02. On 2/7/03, an approvable letter was issued to the sponsor (Elan) noting 2 main clinical concerns (conduct a tyramine sensitivity study and conduct a QTc study) among several other concerns of other disciplines. During the interim, Elan sold this product to another sponsor (Valeant Pharmaceuticals). There have also been interactions between the division and sponsor to provide advice to the sponsor. Most notably, there was a face to face meeting (5/25/04) with Valeant and the DNDP to discuss the study design for the tyramine sensitivity study and the QTc study. The sponsor did not follow much of the advice of the DNDP and markedly altered its study design for the tyramine sensitivity study subsequent to the 5/25/04 meeting. The DNDP had a teleconference with the sponsor to provide additional advice on the tyramine sensitivity study but the sponsor did not inform the DNDP that the tyramine sensitivity study had already been completed at the time that the DNDP was giving advice about how to conduct the study. The sponsor submitted (received 12/16/04) a Response to the Approvable Letter by the new sponsor but this application was not filed because of deficiencies (significant deficiencies and problems related to the navigability of the application, no requested re-analysis of oropharyngeal adverse events, and other more minor ones). The sponsor's response was re-submitted and received by the Agency on 3/20/05 and this response is the subject of this review.

This Executive Summary is organized by presenting a Clinical Comment from the Approvable letter, followed by the Sponsor's Response, followed by Reviewer Comments. I

have provided a brief summary of the tyramine and QTc study designs immediately before the presentation of the respective Clinical Comment requiring the study.

Tyramine Sensitivity Study Design

The sponsor was informed that it needed to conduct a tyramine sensitivity because results of the previous tyramine sensitivity studies were not judged to be reliable. The sponsor conducted a tyramine challenge sensitivity study assessing the effects of 2.5, 5, and 10 mg daily ZS dose groups compared to placebo and phenelzine (15 mg BID, non-specific MAO inhibitor, positive control) in a randomized, double-blinded, placebo-controlled study in which healthy subjects were randomized to the parallel treatment groups. Subjects were challenged with increasing doses of tyramine (25 - 400 mg) at baseline/pre-treatment until subjects showed a threshold response (single ≥ 30 mm Hg increment in SBP). Subjects who showed such a threshold response (≥ 15 mm Hg on 3 consecutive measurements) to tyramine were randomized to one of the 5 treatment groups and were similarly studied for their tyramine threshold response (at least single increment in SBP of ≥ 30 mm Hg) after 11 days treatment.

FDA Clinical Comment in Approval Letter : Need to Conduct Tyramine Challenge Study Assessing Pressor Responses

“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 Zydys 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.”

Valeant Response to Comment : Contradictory results from tyramine challenge Studies

We acknowledge that the results from the prior tyramine-challenge studies are not in full agreement with that published in the medical literature, at least in part due to the study design and lack of adequate controls. Rather than attempt to explain the differences between these studies, we have conducted a new Phase 1 Clinical Study “A Phase 1 Study in Healthy Subjects to Evaluate the Effect of Steady-State Doses of ZELAPARTM (Zydys® Selegiline HCl) on Blood Pressure Responses to Tyramine” (Protocol RNA-ZEL-B21-102) to address the tyramine-pressor effects of ZELAPARTM (Zydys®-selegiline) compared to an active control, NARDIL®. The key pharmacodynamic results of that study are summarized and discussed below.

- This study was a robust evaluation of the potential for ZELAPAR™ to interact with tyramine. The results demonstrate that the clinically recommended dose of ZELAPAR™ 2.5 mg once daily is similar to placebo with regard to its effect on the tyramine pressor response at steady state.
- The active control drug (NARDIL 30 mg) demonstrated a clear positive effect on tyramine pressor response that was comparable to the published results and this effect was substantially higher than that observed with the clinically recommended 2.5 mg ZELAPAR dose. ZELAPAR, at an intermediate dose of 5 mg and at a supratherapeutic dose of 10 mg daily, was shown to enhance the tyramine pressor effect, but the level of effect observed following the 5 mg dose was clinically and statistically significantly lower than that observed with NARDIL 30 mg.
- At two supra-therapeutic doses of 5 mg and 10 mg daily, there was an enhanced tyramine pressor effect, but the effect observed following the 5 mg dose was clinically and statistically significantly lower than that observed with NARDIL 30 mg.

Reviewer Comment

- In general, I agree with the sponsor's above response and comments.
- The data show that the higher doses (5 and 10 mg daily) of ZS showed an increased sensitivity to tyramine relative to increased pressor responses. However, none of the ZS doses (2.5, 5, or 10 mg daily) seemed capable of producing a sustained threshold pressor response (≥ 30 mm increase systolic blood pressure) after challenge with increasing tyramine doses up to 100 mg under fasting conditions more frequently than placebo-treated subjects. In contrast, a substantial percentage of subjects (15 % challenged with 25 mg tyramine and 62 % challenged with 100 mg tyramine) treated with the positive control (phenelzine, non-selective MAO inhibitor) showed sustained threshold pressor responses (2 consecutive ≥ 30 mm increments of systolic blood pressure) after challenge with increasing tyramine doses up to 100 mg under fasting conditions more frequently than placebo-treated subjects (0 %).

A "high" tyramine content oral challenge from food and/or drink is considered to be probably in the range of 40-50 mg tyramine. In addition, administration of a tyramine challenge added to food can be associated with decreased bioavailability of tyramine (including decrease C_{max} , AUC and delayed T_{max}) and decreased pressor responses depending on various conditions. Given that the fasting tyramine study challenge would appear to represent a tyramine challenge under a worst case scenario that could be experienced by eating and/or drinking food or liquid containing 100 mg of readily bioavailable tyramine, I interpret these results as suggesting that none of the daily ZS treatments (2.5, 5, or 10 mg) appear to be associated with a significant risk for a tyramine-induced hypertensive "cheese" reaction. The ZS dose to be approved would be 2.5 mg. The fact that none of the higher doses of ZS (5 and 10 mg daily) appeared to be capable of inducing sustained pressor responses suggests a reasonable margin of safety with respect to a hypertensive risk for patients who might experience a significantly increased pharmacokinetic (PK) exposure (up to an equivalent dose of 10 mg daily) for some reason.

- The sponsor did not conduct a fasting tyramine challenge study as we had recommended (particularly including additional doses at small increments up to 800 mg day and inclusion of a treatment group taking conventional swallowed selegiline 5 mg BID for comparison). Nevertheless, I think that the sponsor's results are adequate and allow us to address the question of whether these doses of ZS appear to be associated with a significant risk for a tyramine-induced hypertensive "cheese" reaction. This most recent study suggested that there appears to be an increased frequency for observing "threshold pressor responses" when a single isolated threshold pressor response is used as the criterion for a threshold response rather than requiring > 2 consecutive blood pressures to achieve the criterion. In retrospect, I consider that results of the sponsor's previous "definitive" fasting tyramine challenge study (AN17933-101) were erroneous and suggested that subjects showing tyramine-induced threshold pressor responses likely represented false positive responses.

QTc Study Design

The sponsor was informed that it needed to conduct a QTc study to characterize or exclude QTc prolongation related to ZS treatment. One randomized, double-blinded, placebo-controlled study showed a mild QTc prolongation associated with ZS treatment when the QTc at the end of the study was compared to the baseline/pre-treatment QTc and results of placebo-treated patients and another identical study did not show such a change.

The sponsor conducted a "thorough" QTc study assessing the effects of 2.5 and 10 mg ZS dose groups were compared to placebo and moxifloxacin in a randomized, double-blinded, placebo-controlled study in which healthy subjects were randomized to the parallel treatment groups. A 12 lead Holter monitor was used to collect electrocardiographic data. Subjects were studied at baseline by collecting 3 ECGs over a short interval at 12 different times over 24 hours and then repeating this ECG collection after treatment on day 12, presumably at PK steady state for ZS.

FDA Clinical Comment in Approvable Letter : Need to Conduct Thorough QTc Study

Clinical Comment : "As with 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."

Valeant Response to Comment: Effect of Selegiline on QTc Prolongation

Although Elan Pharmaceuticals presented an explanation of the inconsistencies in QTc results from Studies 025 and 026, as summarized in ~~the~~ analysis, submitted in the August 7, 2003 amendment to the NDA, Valeant agreed to conduct a definitive QTc study entitled, "A

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Negative and Positive Controlled Evaluation in Healthy Male and Female Subjects of the Potential for ZELAPAR (Zydis® selegiline HCl) at Steady-State to Affect ECG Parameters with Special Emphasis on Cardiac Repolarization” (Protocol RNA600301-101), in accordance with discussions with the Division. The results of that definitive study are reported below.

- The mean maximum on-treatment values for all ECG parameters were within the normal range for all treatment groups. No apparent differences between treatment groups were evident for HR, RR, PR, or QRS. The mean maximum changes from baseline achieved in the ZELAPARTM treatment groups for QT parameters was consistent with those observed for placebo, and less than the mean maximum changes from baseline QT and QTc demonstrated in the moxifloxacin group.
- The maximum change from baseline for QTcI was an increase of approximately 18 msec and 17 msec in the 2.5 mg ZELAPARTM and 10 mg ZELAPARTM groups, respectively, compared to 17 msec in the placebo group and 23 msec in the moxifloxacin group. The increase in QTcI from baseline elicited by administration of moxifloxacin was significantly different from the change from baseline QTcI in the ZELAPARTM treatment groups or placebo. These results validated the sensitivity of this study to detect small changes in QTc intervals.
- Neither the 2.5 mg ZELAPARTM group nor the 10 mg ZELAPARTM group were significantly different from placebo with respect to on-treatment changes in QTcI, nor was any significant difference detected between the two ZELAPAR treatment groups.

Reviewer Comment

- Considering all these results and analyses, critical questions to be answered ultimately are :
 - 1) Does ZS treatment prolong QTc relative to placebo?
 - 2) Is there a gender difference in the magnitude of ZS-related QTc prolongation relative to placebo?
 - 3) If there is a suggestion of a ZS-related QTc prolongation relative to placebo, is there any clinical concern relative to an approval action or labeling based upon the magnitude of the suggested QTc prolongation?
- **Considering all these results and analyses, I still cannot answer question # 1 definitively by noting that ZS does or does not prolong QTc relative to placebo.** Although I agree that this study did not show any statistically significant increments in QTc for ZS relative to placebo, I interpret this “thorough” QTc study as being a “positive” study because it did not exclude a possible increase in QTc below 10 msec. The conservative ANCOVA analysis (using Dunnett’s test) showed that the upper bound of the 95 % CI (one-sided) was ~ 11 secs and the QTc guidance says that the largest time-matched QTc increment of the change from baseline should exclude 10 msec for this upper boundary to be called a “negative” study that exclude this value as a potential risk