CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-479

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review
Complete Response to AE letter

PRODUCT (Generic Name):	ZYDIS® Selegiline HCl
PRODUCT (Brand Name):	ZELAPAR ODT
DOSAGE FORM:	Orally Disintegrating Tablets (ODT)
DOSAGE STRENGTHS:	1.25 mg
NDA:	21-479
INDICATION:	Adjunct treatment for the management of Parkinson's disease in patients who are exhibiting deterioration of response to levodopa/carbidopa therapy
NDA TYPE:	Complete response to AE letter
SUBMISSION DATE:	12/13/05, 2/22/06
SPONSOR:	Valeant Pharmaceuticals International.
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

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EXECUTIVE SUMMARY

In this submission, the sponsor addresses the following ISSUES raised in the approvable letter. The resolution of these issues based on additional information provided by the sponsor is given below:

ISSUE 1: **CYP 450 and selegiline metabolism**

RESOLUTION: Based on Agency's recommendation the sponsor conducted an in-vitro study to evaluate the CYP 450 enzymes involved in the metabolism of selegiline as there were numerous conflicting literature articles on the metabolism of selegiline. The following conclusions can be drawn from this in vitro study:

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

This information will be included in the label.
No new drug interactions studies are warranted.

ISSUE 2: **The potential of selegiline as an inhibitor for CYP450**

RESOLUTION: Selegiline is not an inhibitor of CYP 450 at therapeutic concentrations. (based on previous OCP review by Dr. Andre Jackson as well as some information in this submission)

ISSUE 3: **The potential of selegiline to induce CYP450**

RESOLUTION: The sponsor has given information on the induction potential of selegiline based on a literature article that evaluates the enzyme activity of 7-ethoxycoumarin-deethylation in primary cultured human hepatocytes. 7-ethoxycoumarin-deethylation enzyme reaction is not the ideal way to evaluate induction potential of a drug. Induction potential should be evaluated in human hepatocytes using probe inducers as positive drug controls. Therefore, the induction potential of selegiline is not adequately characterized. Office of Clinical Pharmacology recommends that in vitro induction study using positive controls should be requested as a Phase 4 commitment. In the interim the label should state that the induction potential of selegiline is not known.

ISSUE 4: **Clarification on the effect of hormone replacement (oral contraceptives) on selegiline metabolism**

RESOLUTION:

- 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 sensitive 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 DMS 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)

ISSUE 5: **Effect of hepatic and renal impairment on selegiline plasma concentrations: will a Phase 4 study be acceptable?**

RESOLUTION:

The Agency Medical Officer, Dr. Kapcala 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. (Data given on pages 32-41 of this review)

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. 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 subjects with high AUCs of DMS and L-MA were not the subjects with the longest t1/2, which adds on to the difficulty of interpreting the PK data.

The subjects with the highest Cmax 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. Since the existing data are not scientifically sound; 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 that 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) than the conventional oral tablets..

However, the overall safety from higher exposures at steady state (5-6 fold higher) with supratherapeutic 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.

ISSUE 6: **Discrepancy of food effect of zydis selegiline and that previously known of selegiline**

RESOLUTION: The sponsor has made their best attempt to explain the differences in food effect from that observed in their study versus what was known for oral selegiline. In the Barret study oral selelgiline 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 Cmax's 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 is 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.

The label should include information on what was observed from the ZELAPAR formulation.

ISSUE 7: **Safety update**

RESOLUTION: This will be evaluated by the Medical Officer and is not a part of this review.

RECOMMENDATIONS

The sponsor has responded to all the Agency concerns in the Approvable letter dated September 30, 2005. The complete response is acceptable from the perspective of Office of Clinical Pharmacology, provided the labeling recommendations on page 5 of this review are accepted by the sponsor. The following Phase 4 commitments are requested for ZELAPAR and should be conveyed to the sponsor:

PHASE 4 COMMITMENTS:

1. The sponsor should conduct a pharmacokinetic study in the hepatically impaired subjects. The results of which should be submitted within 1 year of the approval of ZELAPAR. The label should be updated with the results of this study.

2. The sponsor should conduct a pharmacokinetic study in the renally impaired subjects. The results of which should be submitted within 1 year of the approval of ZELAPAR. The label should be updated with the results of this study.
3. The sponsor should evaluate the in vitro induction potential of selegiline based on Agency guidelines on the conduct of such a study. The results of this should be submitted within 1 year of the approval of ZELAPAR. The label should be updated with the results of this study.

Veneeta Tandon, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Ramana Uppoor, Ph.D._____

Director: Mehul Mehta, Ph.D._____

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

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DISCUSSION OF OCP ISSUES IN THE APPROVABLE LETTER

In this submission, the sponsor addresses the following ISSUES raised in the approvable letter:

1. CYP 450 and selegiline metabolism
2. The potential of selegiline as an inhibitor for CYP450
3. The potential of selegiline to induce CYP450

4. Clarification on the effect of hormone replacement (oral contraceptives) on selegiline metabolism
5. Effect of hepatic and renal impairment on selegiline plasma concentrations: will a Phase 4 study be acceptable
6. Discrepancy of food effect of zydis selegiline and that previously known of selegiline
7. Safety update

The sponsor's comment on each of these issues will be discussed in this review, with the exception of safety update.

ISSUE 1: CYP 450 and selegiline metabolism

Phenotyping of P450 isozymes (CYPs) involved in the metabolism of selegiline to desmethylselegiline (DMS) and methamphetamine (MA) was evaluated based on the following assays:

(1) formation of DMS and MA in c-DNA expressed CYPs,
(2) inhibition of DMS and MA formation in human liver microsomes by CYP-selective chemical inhibitors,
(3) inhibition of DMS and MA formation in human liver microsomes by CYP-specific antibodies and
(4) correlation between CYP activities and formation of DMS and MA in human liver microsomes from 15 different donors

The sponsor conducted this in vitro metabolism study according to the Agency's current thinking.

The pathways of metabolism of selegiline as concluded by the sponsor are as follows:

Major pathway: CYP 2B6 and CYP 3A4
Minor pathway: CYP 2A6

The sponsor has concluded this based on in vitro studies (4 different assays) conducted by them.

The isoenzymes evaluated and the concentrations of selegiline studied are given in the following Table 1

Table1: Isoenzymes evaluated in each assay

Assay*	Sel conc.	CYP 450 Isoenzyme evaluated											
	(μM)	1A1	1A2	2A6	2B6	2C8	2C9	2C18	2C19	2D6	2E1	3A4	3A5
1	2	x	x	x	x	x	x	x	x	x	x	x	x
2	1		x	x	x		x		x	x	x	x	
3	2		x	x	x	x			x	x	x	x	
4	1		x	x	x	x	x		x	x	x	x	

*1=recombinant assay: 20 pmol for CYP 3A4 and 10 pmol for other CYPs
2= inhibition by chemical inhibitor (the chemical inhibitor concentrations and the IC50 obtained are shown in Table 3
3=inhibition by antibody
4= correlation analysis

The results from these assays are shown in the following Table (shaded area shows the enzyme involved based on the 4 assays:

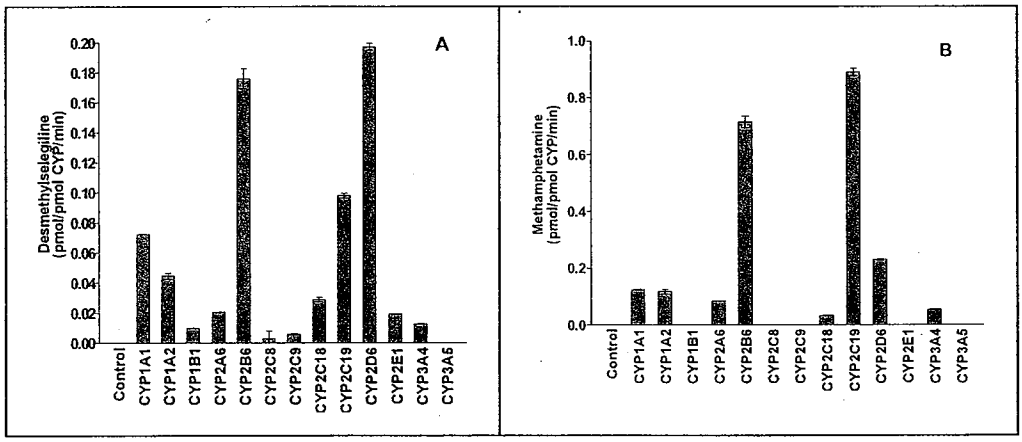
Table 2: Overall results from 4 in vitro assays

CYP Enzymes	c-DNA CYP Enzymes		Human Liver Microsomes					
	Metabolite formed (pmole /min/pmole CYP		Inhibition by chemical inhibitor (IC_{50})(μM)		Inhibition by antibody (% activity remained)		Correlation assay (r^2)	
	DMS	MA	DMS	MA	DMS	MA	DMS	MA
1A2	0.04	0.12	>50	>50	100	90	0.003	0.005
2A6	0.02	0.08	1	0.9	20	22	0.142	0.148
2B6	0.17	0.7	3.5	5.7	13	17	0.769	0.792
2C8	0.003	0	-	-	100	100	0.626	0.619
2C9	0.006	0	>50	>50	-	-	0.008	0.006
2C19	0.10	0.09	>50	>50	89	90	0.005	0.011
2D6	0.19	0.23	>50	>50	100	100	0.126*	0.133*
2E1	0.02	0	>50	>50	92	95	0.103	0.102
3A4	0.01	0.05	2.5	2.6	72	63	0.338	0.349

* The slope was negative.

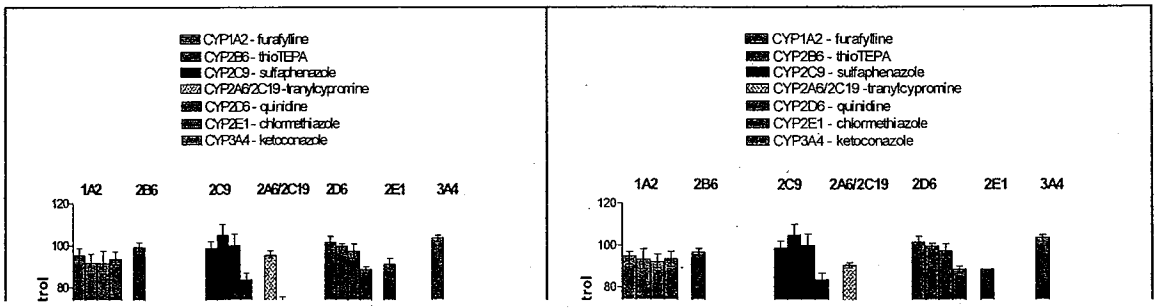
Based on recombinant assay, the following figure shows the formation of metabolite DMS and MA. DMS formation was most evident by CYP 2B6, 2D6 and 2C19 and MA formation was most evident by CYP 2B6, 2C19 and 2D6

Figure 1: Formation of selegiline metabolites by recombinant CYP enzymes (A) desmethylselegiline and (B) methamphetamine.



Based on chemical inhibition assay, the following figure shows that DMS and MA formation was most inhibited by increasing concentrations of CYP specific inhibitors for CYP2B6, 2A6, 3A4 and to a lesser extent by 2E1, but not the other CYPs.

Figure 2: Effect of selective chemical inhibitors on the (A) formation of desmethyl –selegiline, (B) formation of methamphetamine



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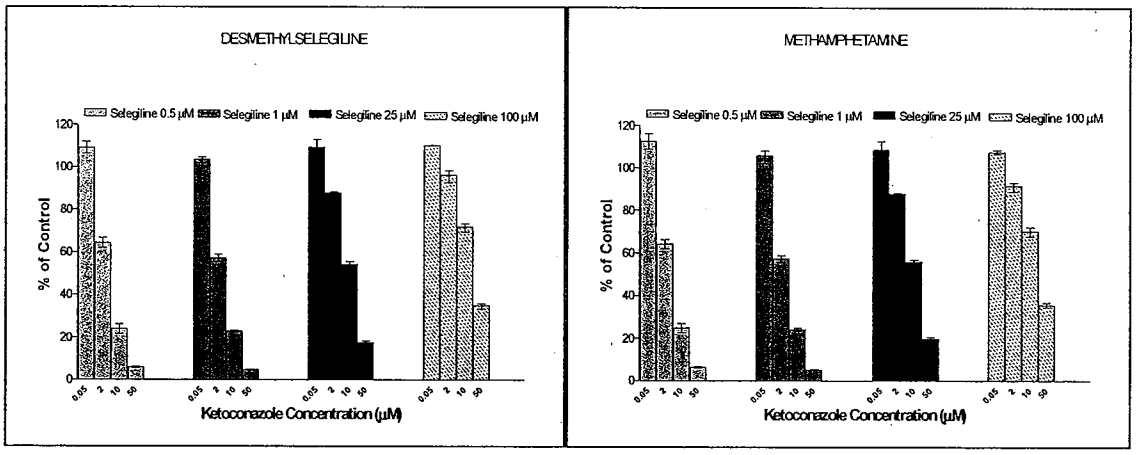
*results are means of triplicate incubations

The inhibition of DMS and MA formations by ketoconazole is dependent on selegiline concentration (see Figure below). IC_{50} for inhibition of DMS formation was estimated to be 2.9, 2.6, 10.7 and 16.5 μM at selegiline concentrations of 0.5, 1, 25 and 100 μM, respectively. IC_{50} for inhibition of MA formation was estimated to be 2.8, 2.6, 11.5 and 22 μM at selegiline concentrations of 0.5, 1, 25 and 100 μM, respectively.

Figure 3: Effect of ketoconazole on the formation of desmethylselegiline and methamphetamine.



Based on inhibition of CYP specific antibody assay, DMS and MA formations were inhibited by antibody against CYP2A6, CYP2B6 and to a lesser extent CYP3A4.

Based on correlation assay, DMS and MA were significantly correlated with CYP2B6 ($r^2 = 0.769$ and 0.792, $p < 0.0001$), CYP2C8 ($r^2 = 0.626$ and 0.619, $p < 0.001$), CYP3A4 ($r^2 = 0.333$ and 0.349, $p < 0.05$), and possibly CYP2A6 ($r^2 = 0.142$ and 0.148, $p < 0.2$). Furthermore DMS formation was significantly correlated with MA formation ($r^2 = 0.99$, $p < 0.0001$), indicating the participation of same P450 isozymes in their formations (see Table below).

Table 3: Correlation assay results

CYP isoform	Enzyme activity	Desmethylselegiline formation*		Methamphetamine formation*	
		r^2	p	r^2	p
CYP1A2	Phenacetin O-deethylase	0.003	0.84	0.005	0.81
CYP2A6	Coumarin 7-hydroxylase	0.142	0.167	0.148	0.157
CYP2B6	(S)-mephenytoin N-demethylase	**0.769**	< 0.0001	0.792	<0.0001
CYP2C8	Paclitaxel 6α -hydroxylase	0.626**	0.0004	0.619**	0.0005
CYP2C9	Diclofenac 4'-hydroxylase	0.008	0.753	0.006	0.776
CYP2C19	(S)-mephenytoin 4'-hydroxylase	0.005	0.813	0.011	0.708
CYP2D6	Bufuralol 1'-hydroxylase	0.126***	0.194	0.133***	0.182
CYP2E1	Chlorzoxazone 6-hydroxylase	0.103	0.242	0.102	0.246
CYP3A4	Testosterone 6β -hydroxylase	**0.333**	< 0.05	0.349	< 0.05
CYP4A11	Lauric acid12-hydroxylase	0.006***	0.786	0.002***	0.874
FMO	Methyl p-Tolyl sulfide oxidase	0.021***	0.611	0.014***	0.671

* DMS formation was significantly correlated with MA formation ($r^2 = 0.99$, $p < 0.0001$), indicating the participation of same P450 isozymes in their formations.

** An internal enzyme activity correlation was found between 2C8 and 2B6 (r^2=0.716), it is difficult to distinguish the involvement of these two isoforms based on the correlation analysis.

*** The correlation was negative.

The conclusions from each of them are shown in the following Table:

Assay	Major enzyme	Minor enzyme
cDNA CYP enzyme	CYP2B6, CYP2C19, CYP2D6	
Inhibition by chemical inhibitor	CYP2B6,CYP2A6, CYP3A4	CYP2E1
Inhibition by antibody	CYP2B6, CYP2A6, CYP3A4	
Correlation assay	CYP2B6, CYP2C8, CYP3A4	CYP2A6

Results of all assays strongly support the involvement of CYP2B6 in the metabolism of selegiline. However it should be pointed that CYP2B6 is a minor P450 isoform and accounted for less than 0.2% of total P450 in the liver.

Although correlation assay suggests that CYP2C8 may be involved in the metabolism of selegiline, results from cDNA expressed CYP enzymes assay and inhibition assays using CYP-specific antibody are not consistent with the result from correlation assay. Since two out of three assays are negative, we therefore conclude that CYP2C8 did not play a significant role in the metabolism of selegiline.

In addition to correlation assay, ketoconazole, a CYP3A4 specific inhibitor gave a low IC_{50} of 2.6 μM for the formation of both DMS and MA, supporting its role in the metabolism of selegiline. Furthermore, addition of CYP-specific antibody also inhibited the formation of both DMS and MA. Thus three out of four assays support the involvement of CYP3A4 in the metabolism of selegiline. It should be pointed out that CYP3A4 is the most abundant isozyme and accounted for at least 30% of total P450 in the liver. Therefore, the sponsor concludes that CYP3A4 participates in the metabolism of selegiline to DMS and MA.

Results of correlation assay suggest the possible role of CYP2A6 in the metabolism. In addition, CYP2A6-specific antibody greatly inhibited the formation of both DMS and MA. It should be pointed out that CYP2A6 is not a major P450 isoform and accounted for only 4% of P450 in the liver. Based on these results, sponsor concludes that CYP2A6 may play a minor role in the metabolism of selegiline.

Literature information on selegiline metabolism

The sponsor has provided additional literature articles on the metabolism of selegiline. Since, the literature articles had conflicting information regarding the major metabolic pathway, the sponsor was recommended to conduct in vitro metabolism studies. The results of which have been summarized in the previous section of this review.

A brief overview of the conclusions of the various authors regarding the involvement of the major and minor CYP isoenzymes in given below. These authors have either used hepatic microsomes with specific inhibitors, correlation study or recombinant assay to determine the metabolic pathway of selegiline. In all in vitro studies, the concentrations of the inhibitors used are much higher than their Ki's. The selegiline concentrations used also are much higher than the therapeutic concentrations.. The conclusions from the various authors are summarized below:

- Taavitsainen et. al (2000): CYP 1 A2 and CYP 3A4 -----major
  CYP 2C19 and CYP 2D6-----not involved
  (This author did not look at CYP2 2B6 as a potential izoenzyme, hence, its role in the metabolism of selegiline cannot be judged from the article)

- Salonen et al (2003): CYP 1A2 and CYP 2B6------major
  CYP 2C19 and CYP 2C8, CYP 3A4-----minor
  CYP 2D6-----not involved

- Wacher et. al (1996): CYP 3A4 -----major
  CYP 1 A2 and CYP 2D6 -----minor
  (This author did not look at any other izoenzyme, therefore the major contribution is in relation to the three izoenzymes evaluated)

- Kamada et. al (2002): CYP 2B6 -----major
  CYP 1 A2, 3A4 and CYP 2C19 -----minor

- Kivistro et. al CYP 3A4----not involved based on an in vivo itraconazole study

- Hidestrad et. al (2001): CYP 2C19 and CYP 2B6------major
  CYP 1 A2 and CYP 3A4 -----minor
  CYP 2D6-----not involved

- Laine et. al (2001) CYP 2C19-----not involved based on 2C19 polymorphism not being important

- Laine et. al showed that subjects on gestodene and ethinyl estradiol had 20-fold higher concentrations of selegiline. Gestodene is known to be a strong mechanism based inhibitor of CYP 3A4. Hence, the discrepancy between the in- vitro findings, a negative in vivo itraconazole study and a positive gestodene study poses conflicting arguments on the involvement of CYP 3A4 as the major metabolizing enzyme.

Based on all these literature articles most authors conclude as follows:

- CYP 2B6 is the major isoenzyme involved in the metabolism of selegiline (concluded by three authors, the other two did not evaluate this isoenzyme as a potential isoenzyme involved in the metabolism of selegiline. The sponsor of this submission also concludes the same.
- CYP 3A4 being one of the major isoenzymes was concluded by two authors. Out of these two authors, one author (Wacher et al) only looked at three isoenzymes, hence overall conclusions cannot be relied upon.
- CYP 3A4 as a minor isoenzyme was concluded by 3 authors. An in vivo itraconazole study (inhibitor of 3A4) was negative suggesting CYP 3A4 to not be a significant isoenzyme involved in the metabolism of selegiline. However, an in vivo gestodene (strong mechanistic based inhibitor of CYP 3A4) study showed significant interaction with selegiline.
- CYP 2C19 was considered a minor isoenzyme by two authors and a major by one author. In vivo study with s-mephenytoin showed 2C19 polymorphism was not impotant. The sponsor observed the involvement of CYP 2C19 only with the recombinant assay, but not the others.
- CYP 1A2 was considered a major isoenzyme by two authors. Selegiline concentrations used in these studies were much higher than the therapeutic concentrations observed (100 µM by Taavitsainen et al an 20-200 µM by Salonen et al)
- CYP 1A2 was considered a minor isoenzyme by three authors. The sponsor did not find CYP 1A2 to be involved by any of the four assays conducted.
- CYP 2A6 was not considered important by all authors. The sponsor suggests this to be a minor isoenzyme.

Based on these overall studies and the sponsor well conducted in vitro study, the reviewer agrees with the sponsor conclusions, which are in away aligned with most literature articles. The only conflicting information remaining is the opposing conclusions of the in vivo itraconazole and gestodene studies. A critical assessment of these studies is given below:

In Vivo Studies to evaluate involvement of CYP 3A4 in the metabolism of selegiline:

REFERENCE: ***In Vivo Itraconazole and selegiline interaction study (Kivisto et. al. Eur J Clin Pharmacol 2001, 57: 37-42)***

Study population: 12 subjects (9M and 3F), age 20-32 years, non smokers, not on oral contraceptives
Study design: randomized, placebo controlled, cross over study with 4 week washout between phases
Itraconazole dose: 200 mg QD for 4 days
Selegiline dose: single 10 mg oral dose on day 4
Results: no effect on the pharmacokinetics of selegiline, DMS, MA, AMP. A single dose caffeine (200 mg) test was also included on day 3 to evaluate the role of CYP 1A2. A statistical significant (p=0.048), but weak (r = 0.41) relationship was found between paraxanthine/caffeine ratio and AUC (DMS)/AUC(SEL)

The authors quote the article by Laine et. al showing a drastic increase in serum selegiline levels with oral contraceptives and conclude that CYP 3A4 inhibiting properties of oral contraceptives are not important in the oral contraceptive-selegiline interaction. The fact that oral contraceptives also inhibit CYP 1A2 may suggest that the probable mechanism of oral contraceptive-selegiline interaction is inhibition of CYP 1A2 mediated biotransformation of selegiline during first pass.

The sponsor did not find CYP 1A2 to be contributing to the metabolism of selegiline.

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.

REFERENCE: ***In-vivo gestodene and ethiny estradiol/levonorgestrel and selegiline interaction study (Laine et. al, Br J Clin Pharmacol, 1999, 47: 249-254)***

Study population: 8F (4 on OC+4 not on OC), age 20-27 years
Oral contraceptive dose: 3 subjects on gestodene 75 µg/ethinylestradiol 30 µg and 1 subject on levonorgestrel 50-125 µg /ethinylestradiol 30-40 µg
Selegiline dose: single dose of 5, 10, 20 and 40 mg
Blood samples: up to 5 hours after drug ingestion
Results: At the 10 mg dose of selegiline, the AUCinf was 20-fold higher and Cmax was 10-fold higher in the group taking OCs. The Tmax was not affected. The t1/2 could not be reliably estimated due to the low concentrations. The AUC values of DMS were somewhat higher in the group using OCs. The magnitude of this increase was much smaller as compared to selegiline and did not reach statistical significance. No significant difference was found for Cmax and Tmax of DMS at all dose levels (data shown on the following page).

Reviewer's Comment:

Meaningful interpretation from this article is difficult because of the following reasons:

- Duration on the oral contraceptives is unknown in this study.
- Plasma samples were only taken till 5 hours post dose. The half life of oral selegiline is ~2 hours. A meaningful estimation of half-life could not be obtained from this study. The t1/2 is used in the calculation of elimination rate constant and in turn for the calculation of AUCinf (reported as AUC in the article). An accurate estimate of AUC cannot be obtained in this study. Hence, the 20-fold higher exposure in subjects on OC may not be accurate. Nevertheless, there was a 10-fold increase in cmax of selegiline as well.
- The number of subjects in this study was 4 and the intersubject variability was extremely high.
- There was a very significant increase in selegiline levels, but an insignificant decrease/change in metabolite DMS level. The other metabolites were not measured in this study. It would be informative to know the effect on other metabolite MA as well to understand the metabolic pathway of selegiline. From this study it appears that the formation of DMS is not dependent on CYP 3A4.
- Overall contribution of the different kinds of OCs (gestodene vs. ethinyl estradiol) is not known from this study. Subjects on OCs were pooled in one category. Gestodene is known to be a potent mechanistic based inhibitor of CYP 3A4. There are some literature articles suggesting that it may be an inhibitor of CYP 1A2 as well. Ethinyl estadiol is a mild inhibitor of both CYP 3A4 and CYP 2B6.
- Also this is not a crossover study, so selegiline PK variability is also a confounding factor.

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Table 1 Pharmacokinetic parameters of selegiline and desmethylselegiline after oral administration of 5, 10, 20 or 40 mg selegiline·HCl to healthy volunteers with no concomitant medication ($n=4$) and with concomitant oral steroids ($n=4$).

	No concomitant medication				*Concomitant oral steroids*			
Parameter	*5 mg*	*10 mg*	*20 mg*	*40 mg*	*5 mg*	*10 mg*	*20 mg*	*40 mg*
Selegiline								
AUC (ng ml^{-1} h)	0.04 (0.04–0.08)	0.5 (0.3–0.7)	0.9 (0.5–2.1)	5.3 (3.4–6.5)	1.8 (0.6–5.3)†	11 (1.5–13)*	22 (16–51)†	89 (51–179)†
95% CI for ratio of means					(11, 131)	(3.6, 54)	(9.7, 70)	(7.5, 42)
C_{max} (ng ml^{-1})	0.05 (0.05–0.2)	0.8 (0.5–1.1)	1.0 (0.6–2.0)	5.4 (1.6–11)	2.8 (1.3–7.5)†	8.9 (2.7–22)*	15 (8.1–44)†	101 (12–203)*
95% CI for ratio of means					(10, 148)	(3.6, 34)	(5.2, 51)	(1.7, 118)
t_{max} (h)	0.75 (0.75–0.75)	0.75 (0.5–1.5)	0.75 (0.5–0.75)	1.3 (0.5–3.0)	0.5 (0.5–0.75)	0.5 (0.5–0.75)	0.5 (0.5–2.5)	0.5 (0.5–0.75)
$t_{1/2}$ (h)	n.a.	n.a.	n.a.	n.a.	n.a.	1.8 (1.5–4.3)[a]	1.4 (1.0–1.9)[a]	1.6 (1.5–2.1)
Desmethylselegiline								
AUC (ng ml^{-1} h)	12 (5.9–18)	31 (23–41)	63 (50–98)	115 (102–151)	18 (12–32)	33 (26–86)	102 (64–138)	269 (178–379)
95% CI for ratio of means					(0.8, 3.6)	(0.6, 2.6)	(0.8, 2.8)	(0.6, 2.9)
C_{max} (ng ml^{-1})	8.6 (2.7–11)	21 (15–27)	39 (27–50)	64 (24–73)	9.4 (7.3–16)	14 (8.5–57)	29 (24–80)	64 (53–114)
95% CI for ratio of means					(0.6, 3.6)	(0.3, 2.5)	(0.5, 1.9)	(0.5, 3.6)
t_{max} (h)	0.75 (0.5–1.0)	0.63 (0.5–1.0)	0.75 (0.5–2.0)	0.88 (0.75–3.0)	0.75 (0.5–1.0)	0.5 (0.5–0.75)	0.75 (0.75–3.0)	0.88 (0.5–2.5)
$t_{1/2}$ (h)	1.4 (1.2–2.7)	1.6 (1.3–1.8)	1.7 (1.6–1.9)	1.5 (1.3–1.7)	1.9 (1.3–3.4)	1.9 (1.8–3.0)	2.1 (1.7–3.0)	2.8 (2.5–5.0)*
95% CI for ratio of means					(0.6, 2.5)	(0.9, 1.9)	(0.9, 1.8)	(1.4, 3.1)

All data are given as median (range); n.a., not assessable; [a]$n=3$; CI, confidence interval. Statistically significant difference compared with the no-concomitant-medication group, *$P<0.05$; †$P<0.001$.

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 selelgiline metabolism are: CYP 2B6 and CYP 3A4
Minor pathway of selelgiline 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.
- In vivo itraconazole, an established CYP 3A4 inhibitor did not show an effect of CYP 3A4.
- Gestodene showed in vivo interaction, but it is known to be a CYP 3A4 and 1A2 inhibitor,

Hypothesis:
Given the lack of effect of CYP 3A4 (based on itraconazole study), could gestodene/ethinyl estradiol effect in fact be on CYP 2B6, which is the major enzyme involved in the metabolism of selegiline? Ethinyl estradiol effect on CYP 2B6 inhibition has been studied by Palovaara et. al in 2003. Gestodene's effect on CYP2B6 is not published in the literature yet and remains unknown.

ISSUE 2: The potential of selegiline as an inhibitor for CYP450

The inhibitory potency of selegiline has been reported by Taavitsainen et al (2000). IC_{50} 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 IC_{50} 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.

Overall Conclusions on ISSUE 2:

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

ISSUE 3: The potential of selegiline to induce CYP450

The sponsor has given information on the induction potential of selegiline based on a literature article, where the author Salonen et al (2003) has looked at enzyme activity of 7-ethoxycoumarin-deethylation in primary cultured human hepatocytes, which is catalyzed by several P450 enzymes including CYP1A2, CYP2A6, CYP2B6, CYP2C8-9, CYP2E1 and CYP3A4/5.

After 48-72 hours of incubation at concentrations of 30 to 1,000 μM, selegiline did not increase enzyme activity of 7-ethoxycoumarin-deethylation. The absence of increases in this reaction suggest that selegiline is unlikely to induce CYP450 enzymes.

Reviewer's comment:

7-ethoxycoumarin-deethylation enzyme reaction is not the ideal way to evaluate induction potential of a drug. Induction potential should be evaluated in human hepatocytes using probe inducer drug (positive drug).

Overall Conclusions on ISSUE 3:

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

ISSUE 4: Clarification on the effect of hormone replacement (oral contraceptives) on selegiline metabolism:

The following is the sponsor's argument regarding clinical relevance of oral contraceptive/hormone replacement therapy and selegiline coadministration.

Since the patient population of Zelapar™ is for the most part expected to be part of the elderly population, the clinical relevance of a concomitant administration of selegiline and oral contraceptives (OCs) is diminished. Therefore the sponsor has focused primarily on the possible interaction of hormone replacement therapy (HRT) and selegiline. The following groups of estrogen and estrogen with progestin therapies for postmenopausal women have FDA-approved labeling:

- Conjugated estrogens
- Drospirenone/estradiol
- Estradiol (including estradiol valerate)
- Ethinyl estradiol/norethindrone
- Levonorgestrel/estradiol
- Medroxyprogesterone/conjugated estrogens
- Norgestimate/estradiol
- Norethindrone/estradiol

The following Table summarizes the information published in the "Drug Information Handbook" (Lacy et al, 2005) regarding an interaction of the above listed individual steroids with the CYPs identified by Valeant to be involved in the metabolism of selegiline; 3A4, 2B6 and 2A6.

Table: FDA-approved steroids for HRT and their interaction with selegiline metabolizing CYPs ("Drug Information Handbook"; Lacy et al, 2005)

Steroid	CYP3A4	CYP2B6	CYP2A6
Conjugated Estrogens	●	○	○
Drospirenone	○ △		
Estradiol	●	○	○
Ethinyl estradiol	● △	△	
Levonorgestrel	●		
Medroxyprogesterone	●		
Norethindrone	●		
Norgestimate	NR	NR	NR

Minor substrate (○), Major substrate (●)
Weak inhibitor (△), Strong inhibitor (▲)
NR: No information available in Lacy et al (2005), but appears to have the potential to interact with CYP3As (Back et al, 1991).

Based upon the summary information in Table 1, most steroid hormones are major substrates for CYP3A4. They have only weak or no inhibitor effects on CYP3A4 and hence have lesser potential to interact with the metabolism of selegiline. The conjugated estrogens and estradiol are classified as weak substrates for both CYP2B6 and CYP2A6. Only ethinyl estradiol and drospirenone have weak inhibition potential for CYP 3A4 and 2B6.

The following literature articles discuss the effect of female sex steroids used for HRT and OC on the pharmacokinetics of selegiline:

REFERENCE: ***Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids (Laine et. al; Br J of Clin Pharm: 47, 249-254, 1999):***

This article has been reviewed under section (please refer to page 21)

Oral contraceptive dose: 3 subjects on gestodene 75 µg/ethinylestradiol 30 µg and 1 subject on levonorgestrel 50-125 µg ethinylestradiol 30-40 µg

This study showed that at the 10 mg dose of selegiline, the AUCinf was 20-fold higher and Cmax was 10-fold higher in the group taking OCs. Three of 4 subjects took gestodene, a strong mechanism-based CYP3A4 inhibitor which affects the metabolism of selegiline.

REFERENCE: ***Effect of concomitant HRT containing estradiol and levonorgestrel on the pharmacokinetics of selegiline: (Palovaara et. al, Eur J Clin Pharm; 2002; 58: 259-263)***

Study population: 12 healthy females, age 20-24 years
Study design: randomized, double-blind, cross-over with 4 weeks wash out
HRT Dose: 2 mg estradiol valerate and 250 µg levonorgestrel or matched placebo for 10 days
Selegiline dose: 10 mg oral dose after an overnight fast, 1 hr after ingesting HRT or placebo
Blood samples: up to 32 hours post dose for selegiline, DMS and MA levels
Results: There was a 59% increase (not statistically significant p=0.14) in AUC of selegiline with no concomitant reduction of metabolite levels. There was a high variability in the data: Two subjects had a three-fold increase in AUC of selegiline and 4 subjects has a decrease in AUC. Cmax of selegiline was not changed and there was a small reduction (-17%) in the Cmax of DMS.

This study shows that HRT preparations containing estradiol valerate and levonorgestrel do not have any significant interaction with selegiline.

REFERENCE: ***Effect of oral contraceptive preparation containing ethinylestradiol and gestodene on CYP3A4 activity as measured by midazolam 1'-hydroxylation; (Palovaara et.al Br. J Clin Pharm: 2000, 50-333-337):***

Study population: 9 healthy females, age 20-25 years
Study design: randomized, double-blind, cross-over
OC Dose: 30 µg ethinyl estradiol and 75 µg gestodene or matched placebo for 10 days
Midazolam dose: 7.5 mg oral dose after a overnight fast, 1 hr after ingesting OC or placebo
Blood samples: up to 24 hours post dose for midazolam and 1-hydroxy midazolam levels
Results: The combined OC increased the mean AUC of midazolam by 21% and decreased that of 1'-hydroxy midazolam by 25%

Reviewer's Comment:

The results of this study show that gestodene did not have a drastic effect on a CYP 3A4 substrate (midazolam) in this case as seen with the interaction of gestodene/ ethinyl estradiol (N=3) and selegiline (Laine et. al, 1999). The above three studies are done by the same group of

scientists. It is well known the gestodene is a strong mechanism based inhibitor of CYP 3A4. Hence, the article by Laine et. al suggested that selegiline could likely be metabolized by CYP 3A4. However, the same magnitude (20-fold) was not seen in the case of another sensitivesubstrate of CYP 3A4. This to me suggests that gestodene may also be an inhibitor of other CYP enzymes not known yet. There are some recent (Gansfors et. al 2005; Clinical Pharmacology and Therapeutics; 78(4) 400-11) suggestions of gestodene inhibiting CYP 1A2 mediated metabolism. In the light of these recent findings, it could be possible that gestodene inhibits CYP 2B6 (major metabolite of selegiline), not known yet.

REFERENCE: ***Inhibition of CYP 450 activity by HRT and OC as measured by bupropion hydroxylation: (Palovaara et.al Clin Pharm Ther 2003; 74:326-33)***

Study population: 12 healthy females, age 20-25 years
Study design: randomized, double-blind, 3-way cross-over
OC Dose: 2 mg estradiol valerate and 250 µg levonorgestrel (HRT) or 30 µg ethinyl estradiol and 150 µg desogestrel (OC) for 10 days
Bupropion dose: 150 mg sustained release oral dose in the Phase 1 (pre-treatment) and 1 hr after the last HRT dose in phase 2 and 3
Blood samples: up to 72 hours post dose for bupropion and hydroxybupropion levels
Results: 10-day administration of HRT reduced the hydroxybupropion/bupropion AUC ratio by 49% as a result of 47% decrease in AUC of hydroxybupropion. The AUC of hydrobupropion was increased by 64%. The AUC of hydroxyl búpropion was reduced to a lesser extent (31%) after OC treatment with a simultaneous reduction in bupropion AUC. This suggests that HRT inhibited the CYP 2B6 catalyzed hydroxylation of bupropion, where as combination oral contraceptive had a modest effect on CYP 2B6 activity. It also seems to have an induction effect because the bupropion levels reduced as well. OCs inducing CYP 2B6 is not known yet.

Reviewer's Comment:

It is interesting to note that estradiol valerate and levonorgestrel (HRT) seemed to inhibit the CYP 2B6 mediated hydroxylation of bupropion (a strong CYP 2B6 substrate), but according to Lacy et al Handbook (see previous Table), neither of these are inhibitors of CYP enzymes (2B6 or 3A4). Both are major substrates for CYP 3A4, hence a major interaction should be unlikely.

Ethinyl estradiol and desogestrel (OC) both have weak inhibition potential for CYP 2B6/CYP 3A4 and CYP 3A4 alone, respectively. In this study this combination of OC showed a modest inhibition (31%) of hydroxylation of bupropion.

It should be noted that the same combination and same dose of HRT was used to evaluate an interaction with selegiline by the same group and authors and no significant interaction was observed.

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.

comparative exposure levels and other pharmacokinetics related arguments will be discussed in this review.

The sponsor also acknowledges that there is a small fraction of subjects 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. The sponsor proposes the following language be added in the package insert: "**Zelapar should be used with caution in patients with a history of or suspected severe renal or hepatic disease**".

The sponsor believes that the renal and hepatic impairment studies should be conducted Phase 4.

Sponsor's critical assessment of the Antilla et. al article has the following key points (given as circled bullets), followed by reviewer's comment for each of sponsor's critical assessments:

- Antilla et. al used a 20 mg oral dose of selegiline. The sponsor argues that the 20 mg dose is 8 times the proposed Zelapar dose. They also argue that based on a study in 4 subjects by Laine et al (1999), the pharmacokinetics of selegiline were more than dose proportional, hence the AUC reported with the 20 mg oral dose may significantly overstate the AUC following a 2.5 mg/day Zelapar dose.

  Reviewer's Comment:

  The dose argument does not hold true because the Zydis dose (1.25 mg) was selected to give equivalent exposure to the Eldepryl dose 10 mg . The Table with the PK parameters after 5, 10, 20 and 40 mg oral dose from the article of Laine et. al (1999) is given on page 22 of this review which the sponsor quotes for dose proportionality. There were only 4 subjects in this study and the PK of selegiline is highly variable. From Laine's data the 10 and 20 mg doses seem to be dose proportional, but the 5 and 10 mg dose are not and similarly the 20 and 40 mg doses are not. Hence it is difficult to assess dose proportionality given the small number of subjects and the high variability. Selegiline however, is likely to be non-linear at higher doses based on greater than predicted accumulation after multiple doses.

- Examination of the mean results and standard deviations for either the Cmax or AUC parameters in the Anttila et al (2005) article, document the large inter-subject variation (greater than 100% of the mean) observed in both the hepatic and renal impaired populations. Combined with a relatively small sample size (n=10), the comparisons using mean data may be misleading. Only 4 of 10 of the hepatic impaired patients and 3 or 4 of the 10 renal impaired patients had higher serum concentration-time profiles compared to the healthy subject population, suggesting that only a fraction of the hepatic and renal impaired population experienced an elevation in selegiline plasma concentrations. (Figure given below)

  Reviewer's Comment:

  The variability observed and the number of subjects showing the increase is true. Discussions on the nature of the impairment in those 3-4 subjects that do show the increase is given else where in this review.

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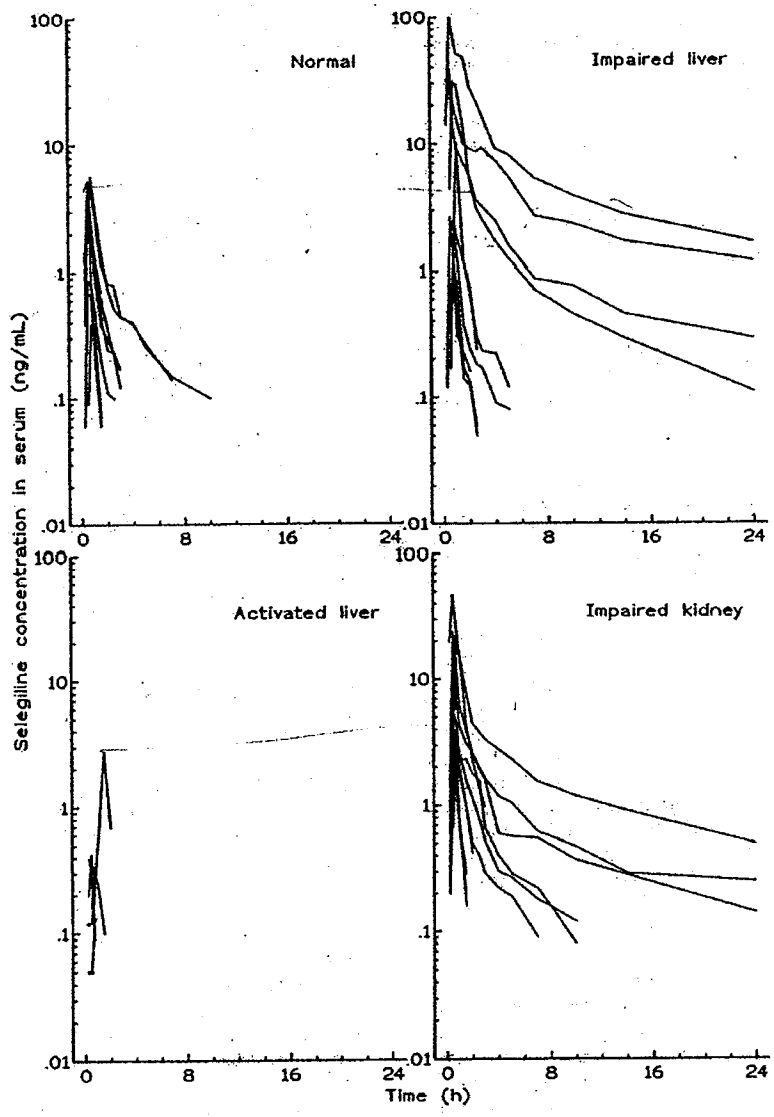

- The critical parameter used for comparison by Anttila et al (2005) is the area under the concentration-time curve, AUC. In order to estimate the AUC following a single dose, as was done by Anttila, it is imperative that the half life of unchanged selegiline be accurately measured (Purves, 1992). Anttila reports in his article that "The half-life of unchanged selegiline could not be reliably estimated." The inability to reliably estimate half-life, directly impacts the validity of the calculation of $AUC_{0-\infty}$, the parameter used by Anttila to assess the influence of hepatic or renal disease on selegiline pharmacokinetics. Although this does not discount there was an effect of hepatic and renal disease on selegiline pharmacokinetics, it does question the accuracy of the reported results.

Reviewer's Comment:

Agree. The sponsor does acknowledge that this does not discount there was an effect of hepatic and renal disease on selegiline pharmacokinetics, it does question the accuracy of the reported results.

- The metabolic profile of selegiline following oral dosing with Eldepryl® is different than for buccally-absorbed Zelapar™ (Zydis selegiline). Orally administered selegiline undergoes extensive metabolism in the gut and liver, with low bioavailability estimated at 10%, with only 0.01% to 0.3% excreted in the urine as unchanged selegiline. In contrast, approximately 30% of Zelapar™ is absorbed through the buccal mucosa, and undergoes metabolism after reaching the systemic circulation, bypassing both the gut and first-pass hepatic metabolism.
- With respect to the relative exposure of oral vs. buccally absorbed selegiline, the increase in systemic exposure due to liver dysfunction would be considerably less for Zelapar™ than for the selegiline product used in the Anttila et al (2005) study. This is due to the reduced 'first pass' metabolism resulting from absorption of Zelapar™ in the oral cavity.
- [redacted] provided the scientific basis for the markedly lower influence of hepatic impairment on the systemic exposure of selegiline following buccal absorption compared to traditional oral administration. As presented in his assessment, [redacted] concluded that following buccal absorption, which bypasses both gut wall metabolism and hepatic first pass effects, selegiline systemic exposure (AUCτ) would increase only by a factor of 3.25, due to the relative reduction in hepatic clearance. He further states "this is a conservative estimate" due to the simplified calculations not taking into account the contribution of gut-wall metabolism of selegiline following oral administration. While a 3.25 fold increase is certainly noteworthy, it is by far lower than the 18 fold increase following the administration of conventional selegiline tablets reported by Anttila et al (2005).

b(4)

b(4)

Reviewer's Comment:

The above three arguments by the sponsor deal with the buccal absorption of Zydis selegiline and the quantitative difference of metabolism with this dosage form. It is true that Zelapar would by pass gut and first pass metabolism and the quantitative levels of the metabolites seen with Zelapar are much less than that seen with oral selegiline. Oral selegiline is more extensively metabolized. [redacted] calculations are based on the assumption of linear PK, which is not true in the case of selegiline. Hence, the figure 3.25 fold may not necessarily be true. However, the reviewer agrees that the extent of exposure seen with the liver impaired subjects will be less than that with oral selegiline.

b(4)

- Anttila et al (2005) did not specify the degree of hepatic disease in the liver disease patients. [redacted] an experienced hepatologist well-established in drug metabolism and disposition research points out in his written opinion that the liver impaired patients studied by Anttila probably had cirrhosis, as "liver dysfunction that had been confirmed histologically" can only be inferred from a liver biopsy if cirrhosis is present. In addition, the presence of mildly elevated serum aminotransferases, with mean AST higher than mean ALT, is characteristic of stable cirrhosis.

  After contacting one of the co-authors of the Anttila et al (2005) study, [redacted] 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.

b(4)

b(4)

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.

Reviewer's Comment: NOT FOR PUBLIC DISCLOSURE within brackets

[.....The Agency Medical Officer, Dr. Kapcala also was able to contact the author and get additional information on the laboratory parameters determining the degree of liver and renal impairment in these 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 study). In addition to this, individual subject PK parameters were also obtained from the authors. (Data attached at the end of this comment)

For liver impairment, the two subjects with the high levels of serum bilirubin were not the subjects with the highest exposure of selegiline, in fact one of them had very low exposure to selegiline. Only one subject out of 10 seemed to have high (3-5 times the upper limit of normal) values of AST and ALT. This subject did not have the highest exposure of selegiline. Interestingly enough this subject had the highest concentration of desmethylselegiline (DMS) and l-methamphetamine (L-MA). One of the subject with high level of bilirubin also had high exposure to DMS, suggesting that liver impairment in this case 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 t1/2, which adds on to the difficulty of interpreting the PK data.

The subject with the highest Cmax 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 consistent 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. However, this was not the case. 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....]

Individual subject data obtained from Antilla et. al: **NOT FOR PUBLIC DISCLOSURE**

Table 1. Diagnosis and prestudy laboratory test (serum chemistry: liver function) results in subjects with impaired liver function

Subject #	Diagnosis	AST (U/L)	ALT (U/L)	APL (U/L)	GGT (U/L)	PIIINP (µg/L)
3	Fatty liver + fibrosis	21	29	228	142	5.9
4	Liver cirrhosis	48	47	223	138	10.2
7	Liver cirrhosis	34	25	198	78	6.9
9	Liver fibrosis	24	61	168	98	2.8
10	**Liver cirrhosis**	**123**	**206**	694	1440	6.2
11	Liver fibrosis	28	49	141	46	4.1
12	Liver cirrhosis	47	38	175	139	2.6
14	Fatty liver + fibrosis	39	60	216	37	4.5
15	Liver cirrhosis	37	36	159	165	7.2
39	Liver fibrosis	63	90	329	261	4.3
Reference values		10-35	10-35	50-200	5-50	1.7-4.2

Table 2. Prestudy laboratory test results from subjects with impaired liver function

Subject #	Diagnosis	Serum albumin (g/L)	Serum bilirubin ((µmol/L)
3	Fatty liver + fibrosis	39	9
4	**Liver cirrhosis**	**37**	**61**
7	Liver cirrhosis	35	17
9	Liver fibrosis	41	20
10	Liver cirrhosis	41	20
11	Liver fibrosis	39	9
12	Liver cirrhosis	38	19
14	**Fatty liver + fibrosis**	**46**	**44**
15	Liver cirrhosis	38	13
39	Liver fibrosis	36	8
Reference values		35-50	< 20

Table 3. Diagnosis and prestudy laboratory test (serum chemistry: kidney function) results in subjects with impaired kidney function

Subject #	Diagnosis	urea (mmol/L)	creatinine (µmol/L)
21	Reduced kidney function	11.7	144
22	Reduced kidney function	8.4	151
23	Reduced kidney function	7.2	124
24	Nephropathia diabetica	12.2	132
25	**Nephropahia diabetica**	**16.6**	**237**

27	Neprophathia	9.1	134
28	Nephropathia	-	127
29	Nephropahtia	8.1	128
41	Reduced kidney function	8.6	116
42	**Nephropathia diabetica**	**32.0**	**494**
Reference values		1.7-8.3	55-115

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Study: Effect of liver and kidney function on the pharmacokinetics of selegiline

Table 1

C_{max} (ng/mL) of selegiline

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	3.74	3	2.50	13	< 0.05	21	5.74
2	4.63	4	38.8	16	0.40	22	23.7
5	0.88	7	103.	17	0.12	23	21.8
6	0.68	9	1.13	18	0.31	24	3.42
30	4.77	10	30.8	19	< 0.05	25	3.99
32	5.75	11	1.93	20	0.21	27	4.46
34	5.26	12	0.86	31	0.13	28	18.6
35	2.62	14	10.20	33	0.13	29	2.64
37	2.71	15	31.5	36	0.41	41	2.06
38	0.39	39	2.67	40	0.43	42	46.8
Mean	3.14		22.34		0.21		13.32
SD	1.99		31.95		0.16		14.49

Table 2

t_{max} (h) of selegiline

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	0.5	3	0.75	13	-	21	0.5
2	0.75	4	0.5	16	0.25	22	0.5
5	0.5	7	0.5	17	0.25	23	0.75
6	0.75	9	0.75	18	0.75	24	0.5
30	0.5	10	0.75	19	-	25	0.75
32	0.75	11	0.5	20	0.5	27	0.5
34	0.5	12	0.75	31	0.75	28	0.5
35	0.5	14	1	33	0.5	29	0.75
37	0.5	15	0.5	36	0.5	41	1
38	0.75	39	0.5	40	0.5	42	0.5
Median	0.5		0.63		0.5		0.5
Range	0.5-0.75		0.5-1		0.25-0.75		0.5-1

Study: Effect of liver and kidney function on the pharmacokinetics of selegiline

Table 3

AUC (ng h/mL) of selegiline

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	1.55	3	2.94	13	0	21	7.42
2	6.25	4	157.31	16	0.20	22	80.81
5	0.85	7	240.38	17	0.03	23	17.64
6	0.45	9	0.82	18	0.27	24	1.86
30	3.37	10	43.29	19	0	25	3.72
32	6.81	11	2.27	20	0.29	27	2.12
34	4.06	12	0.64	31	0.03	28	21.59
35	2.13	14	6.01	33	0.05	29	6.90
37	2.31	15	49.35	36	0.17	41	1.81
38	0.30	39	1.34	40	0.16	42	73.22
Mean	2.808		50.435		0.120		16.709
SD	2.303		82.633		0.111		22.170

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Study: Effect of liver and kidney function on the pharmacokinetics of selegiline

Table 4

C_{max} (ng/mL) of desmethylselegiline

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	55.2	3	33.2	13	12.9	21	57.2
2	54.0	4	1.79	16	19.1	22	45.6
5	41.2	7	14.0	17	10.2	23	43.4
6	33.1	9	39.4	18	37.8	24	39.4
30	64.6	10	80.8	19	10.0	25	30.3
32	46.1	11	35.1	20	27.6	27	70.0
34	58.8	12	35.1	31	19.4	28	54.8
35	49.2	14	40.0	33	29.2	29	31.1
37	55.6	15	23.8	36	14.8	41	23.3
38	30.1	39	27.0	40	31.7	42	38.2
Mean	48.79		33.02		21.27		43.33
SD	11.18		20.65		9.74		14.15

Table 5

t_{max} (h) of desmethylselegiline

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	0.5	3	1	13	0.75	21	0.75
2	0.75	4	1	16	0.75	22	0.75
5	0.75	7	1	17	0.5	23	1
6	0.75	9	1	18	1	24	0.5
30	0.75	10	1	19	0.5	25	0.75
32	0.75	11	0.75	20	1	27	0.75
34	0.5	12	0.75	31	1	28	0.5
35	0.75	14	1	33	0.5	29	1.5
37	0.75	15	0.5	36	0.75	41	1.5
38	1	39	0.75	40	0.5	42	0.5
Median	0.75		1		0.75		0.75
Range	0.5-1		0.5-1		0.5-1		0.5-1.5

Study: Effect of liver and kidney function on the pharmacokinetics of selegiline

Table 6

AUC (ng h/mL) of desmethylselegiline

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	80.17	3	93.91	13	15.61	21	152.68
2	153.65	4	4.66	16	22.56	22	191.81
5	82.70	7	110.77	17	7.97	23	167.08
6	52.91	9	89.49	18	72.39	24	73.75
30	117.50	10	236.22	19	7.66	25	82.42
32	123.36	11	73.04	20	72.91	27	120.76
34	117.16	12	62.06	31	26.65	28	196.55
35	123.60	14	118.48	33	41.00	29	143.21
37	105.66	15	73.93	36	17.11	41	56.97
38	58.48	39	29.23	40	30.51	42	224.81
Mean	101.52		89.16		31.27		141.00
SD	32.02		62.32		23.95		56.70

Table 7

Half-life (h) of desmethylselegiline

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	2.29	3	7.13	13	0.78	21	10.05
2	7.19	4	4.04	16	1.48	22	12.48
5	6.55	7	26.48	17	0.55	23	10.31
6	1.71	9	6.11	18	10.00	24	3.26
30	8.42	10	18.36	19	1.93	25	4.97
32	5.38	11	4.43	20	2.35	27	6.12
34	6.13	12	2.64	31	1.05	28	8.11
35	6.60	14	19.46	33	1.47	29	11.17
37	4.09	15	15.66	36	0.60	41	6.52
38	2.59	39	1.35	40	1.53	42	11.40
Mean	5.09		10.57		2.17		8.44
SD	2.30		8.68		2.81		3.10

Study: Effect of liver and kidney function on the pharmacokinetics of selegiline

Table 8

C_{max} (ng/mL) of *l*-methamphetamine

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	43.1	3	19.2	13	33.7	21	34.0
2	27.7	4	3.49	16	24.3	22	18.4
5	22.7	7	9.66	17	17.5	23	15.3
6	21.6	9	20.0	18	42.5	24	22.1
30	22.6	10	31.2	19	32.5	25	27.3
32	27.4	11	17.8	20	36.0	27	24.4
34	20.2	12	20.4	31	15.4	28	26.3
35	22.5	14	-	33	26.6	29	29.3
37	41.1	15	13.1	36	28.4	41	19.8
38	27.5	39	21.7	40	28.6	42	17.1
Mean	27.64		17.39		28.55		23.40
SD	8.09		7.91		8.23		5.93

Table 9

t_{max} (h) of *l*-methamphetamine

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	3	3	2	13	5	21	1.5
2	0.75	4	10	16	3	22	3
5	2.5	7	3	17	7	23	2
6	2.5	9	3	18	2.5	24	2.5
30	1.5	10	2	19	1.5	25	2
32	3	11	2	20	2	27	0.75
34	1	12	2	31	2	28	2.5
35	3	14	-	33	2.5	29	3
37	2	15	4	36	3	41	3
38	1.5	39	3	40	0.75	42	1
Median	2.25		3		2.5		2.25
Range	0.75-3		2-10		0.75-7		0.75-3

Study: Effect of liver and kidney function on the pharmacokinetics of selegiline

Table 10

AUC (ng h/mL) of *l*-methamphetamine

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	687.8	3	595.9	13	818.2	21	1398.8
2	659.2	4	180.2	16	547.0	22	839.7
5	522.7	7	310.9	17	536.3	23	532.7
6	572.9	9	354.0	18	669.0	24	811.4
30	390.7	10	820.3	19	450.1	25	1240.1
32	627.1	11	323.9	20	985.9	27	690.7
34	321.6	12	735.0	31	261.0	28	1210.9
35	578.6	14	-	33	470.4	29	1239.3
37	812.9	15	354.2	36	522.8	41	562.8
38	545.0	39	499.1	40	493.7	42	1047.1
Mean	571.85		463.74		575.44		957.33
SD	141.75		214.13		28.55		310.73

Table 11

Half-life (h) of *l*-methamphetamine

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	12.2	3	24.2	13	13.9	21	30.5
2	18.9	4	31.3	16	12.5	22	27.9
5	14.9	7	22.9	17	19.7	23	19.2
6	14.2	9	13.0	18	10.3	24	22.7
30	12.3	10	25.0	19	11.1	25	31.4
32	15.0	11	14.4	20	17.1	27	24.9
34	10.2	12	20.0	31	9.2	28	28.9
35	18.1	14	-	33	10.9	29	23.0
37	9.7	15	15.8	36	9.8	41	18.8
38	14.8	39	16.7	40	12.2	42	54.8
Mean	14.04		20.37		12.69		28.21
SD	3.03		5.99		3.36		10.33

Study: Effect of liver and kidney function on the pharmacokinetics of selegiline

Table 12

Cmax (ng/mL) of *l*-amphetamine

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	13.2	3	4.8	13	17.4	21	-
2	5.9	4	1.8	16	7.5	22	4.9
5	6.2	7	2.9	17	7.4	23	4.0
6	7.7	9	5.5	18	18.4	24	8.6
30	6.5	10	6.2	19	21.1	25	-
32	12.4	11	5.0	20	18.0	27	6.0
34	11.9	12	7.0	31	7.5	28	6.7
35	8.6	14	-	33	12.2	29	7.7
37	12.1	15	6.7	36	17.9	41	4.6
38	10.7	39	5.2	40	18.1	42	5.1
Mean	9.52		5.01		14.56		5.92
SD	2.84		1.71		5.34		1.62

Table 14

t_{max} (h) of *l*-amphetamine

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	3	3	7	13	5	21	-
2	10	4	14	16	3	22	14
5	4	7	7	17	1.5	23	10
6	10	9	4	18	2.5	24	2.5
30	2	10	5	19	1.5	25	-
32	3	11	3	20	3	27	1
34	2.5	12	10	31	1.5	28	10
35	5	14	-	33	2.5	29	7
37	4	15	1.5	36	0.75	41	14
38	1.5	39	1.5	40	5	42	24
Median	3.5		5		2.5		10
SD	1.5-10		1.5-14		0.75-5		1-24

Study: Effect of liver and kidney function on the pharmacokinetics of selegiline

Table 14

AUC (ng/mL) of *l*-amphetamine

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	260.6	3	181.1	13	441.4	21	-
2	311.8	4	119.9	16	164.2	22	370.6
5	198.7	7	275.0	17	251.6	23	261.0
6	278.3	9	122.2	18	332.4	24	588.3
30	204.2	10	176.5	19	344.9	25	-
32	451.4	11	130.4	20	442.6	27	335.7
34	325.2	12	250.0	31	156.8	28	758.6
35	213.6	14	-	33	216.8	29	425.6
37	282.9	15	191.1	36	334.1	41	210.5
38	345.7	39	228.3	40	237.1	42	351.7
Mean	287.24		186.07		292.20		412.77
SD	77.02		56.42		103.33		179.68

Table 15

Half-life (h) of amphetamine

Normal		Impaired liver		Activated liver		Impaired kidney	
Subj		Subj		Subj		Subj	
1	16.0	3	18.1	13	16.6	21	-
2	28.2	4	42.8	16	12.5	22	48.4
5	15.2	7	67.6	17	21.1	23	38.0
6	17.8	9	15.3	18	9.4	24	44.9
30	18.8	10	26.5	19	8.4	25	-
32	20.0	11	18.4	20	13.0	27	36.5
34	15.3	12	18.0	31	11.7	28	66.9
35	14.9	14	-	33	11.4	29	35.1
37	19.1	15	17.2	36	12.2	41	28.0
38	19.4	39	29.9	40	8.2	42	37.6
Mean	18.48		28.21		12.46		41.92
SD	3.94		17.17		3.91		11.83

Additional rationale from the sponsors for evaluating pharmacokinetics in the hepatic and renal patients Phase 4:

- Calculated theoretical potential accumulation following oral buccally absorbed Zelapar™ will be much lower, estimated to be 3-5 fold and not 18 fold as it has been reported by Anttila et al (2005) following the administration of 20 mg of the conventional selegiline tablet formulation, Eldepryl®.

  AUC ratios for metabolites and selegiline ranged from 3 to 8 after buccal dosing of Zelapar™ 2.5 mg QD versus ratios of 10 to 31 after oral dosing of Eldepryl® BID, indicating that oral dosing of selegiline had about a 3.3 fold higher metabolic rate compared with buccal dosing of selegiline. Correcting for the difference in the metabolic rate between these two products, we have therefore estimated that the plasma selegiline AUCs in liver impaired patients in the Anttila study would be reduced from a 18 times increase over control for oral dosed Eldepryl® to an approximately 5.5 times increase (18/3.3) for buccal dosed Zelapar™. Assuming the effects of renal impairment are similar on the pharmacokinetics of selegiline for Eldepryl® 5 mg BID and Zelapar™ 2.5 mg, selegiline, AUC in renal impaired patients could increase as high as 6 times based on the results by Anttila et al (2005) following the administration of Zelapar™.

  Zelapar™ 2.5 mg QD steady-state plasma mean AUCτ ranges from 2.84 ng.h/mL to 6.52 ng.h/mL in healthy subjects, a steady-state plasma AUCτ of 17.0 ng.h/mL to 39.1 ng.h/mL and 15.6 ng.h/mL to 35.9 ng.h/mL would be obtained in renal and hepatic impaired patients, according to the findings by Anttila et al (2005). Although, these possible increases of selegiline systemic exposure are significant, similar and higher selegiline AUCτ have been found in other studies.

  The sponsor quotes the values from the following studies:

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Table . Selegiline $Cmax_{ss}$ and AUCτ from Clinical Studies included in NDA 21-479

Study	Dose (mg) Zelapar™	Mean $Cmax_{ss}$ (ng/mL)	Mean AUCtau (ng.h/mL)
AN17933-101	1.25	3.96 (1.28-6.97)	4.77 (1.46-6.82)
	2.5	4.37 (1.84-6.95)	6.52 (2.41-13.9)
	5	5.54 (1.63-10.0)	8.51 (4.39-13.2)
	Eldepryl® 5 BID	1.73 (0.5-4.11)	8.32 (1.59-15.1)
Z/SEL/95/007	10	19.79 (9.65-31.5)	39.77 (22.5-59.0)
	Deprenyl 10 QD	4.61 (0.38-12.4)	10.56 (0.81-29.7)
Z/SEL/96/014	1.25	3.38 (1.14-5.83)	6.39 (1.94-12.3)
	Eldepryl® 10 QD	4.15 (0.98-8.73)	11.41 (2.74-33.8)
RNA-ZEL-B21-102	2.5	1.81 (0.26-2.91)	5.04 (0.31-9.75)
Tyramine Pressor	5	3.55 (2.14-6.81)	12.5 (6.36-27.5)
	10	7.92 (3.74-15.6)	26.1 (13.0-52.3)
RNA600301-101	2.5	1.1 (0.14-2.41)	2.84 (0.378-6.45)
QTc	10	5.44 (1.27-13.4)	17.6 (4.28-33.5)
Z/SEL/97/025	1.25	ND	3.33 (median)
Z/SEL/97/026	2.5	ND	6.66 (median)
Phase 3			
Z/SEL/95/008	1.25	2.22 (0.29-6.18)	ND
Phase 3	10	7.73 (0.62-22.3)	ND
	Eldepryl® 10 QD	2.54 (0.09-38.9)	ND

Reviewer's Comment:

Zydis selegiline 1.25 mg dose was chosen because a 1.25 mg dose produced equivalent exposure to 10 mg oral selegiline. It is true that the 18-fold increase observed in the Antilla paper is with a 20 mg oral dose and the accumulation predicted for a 1.25 mg Zydis dose will naturally be lower (1.25 mg designed to produce exposure equivalent to 10 mg Eldepryl) than the 18-fold. However, the theoretical calculations are based on the assumption that the PK of selegiline is linear, which is not true. Additionally the theoretical calculations are also based in the metabolite ratios given above. Theoretical calculations based in linear PK assumption is not applicable for selegiline that has a non-linear PK, however, the calculations based on metabolite ratios seem reasonable and demonstrate that the increases observed with Zelapar will be relatively less compared to Eldepryl.

The reviewer agrees that there is a lot of variability (~100%) in the PK parameters across studies and within subjects.

- Zelapar™ 10 mg led to a 4.9 fold increased mean $Cmax_{ss}$ selegiline and a 6.3 fold increased mean AUCτ compared to the therapeutic dose Zelapar™ 2.5 mg without a clear signal of QTc prolongation.

Reviewer's Comment:

This is a true observation. Medical officer should comment on the projected risk, if any.

- The supratherapeutic dose of Zelapar™ 10 mg, which was accompanied by an approximately 5 fold increased mean AUCτ compared to the therapeutic dose Zelapar™ 2.5 mg did not lead to a significantly different minimum threshold dose of tyramine necessary to produce a predefined ≥ 30 mmHg increase in SBP, as seen in the table below.

Table. The Relationship between TYR30 "15-30", Selegiline $Cmax_{ss}$ and AUCτ for the Zelapar™ 2.5 mg, 5 mg, and 10 mg

	Zelapar™ 2.5 mg			**Zelapar™ 5.0 mg**			**Zelapar™ 10 mg**			**Placebo**
	$Cmax_{ss}$ (pg/mL)	AUCτ (pg.hr/ mL)	TYR30 (mg)	$Cmax_{ss}$ (pg/mL)	AUCτ (pg.hr/ mL)	TYR30 (mg)	$Cmax_{ss}$ (pg/mL)	AUCτ (pg.hr/ mL)	TYR30 (mg)	TYR30 (mg)
Mean	1813.4	5040	196.9	3554.3	12518.6	259.4	7921.3	26125	200	316.7
SD	858.1	3287.1	143.0	1350.6	5523.2	135.8	3556.7	12949	110.8	132.3
Range	263.5-2914.6	310.1-9754.7	25-400	2147.0-806.3	6362.9-27544	12.5-400	3740.5-15574.4	13050-52286	50-400	50-400

Reviewer's Comment:

This is a true observation. The Medical officer should comment on the projected risk, if any.

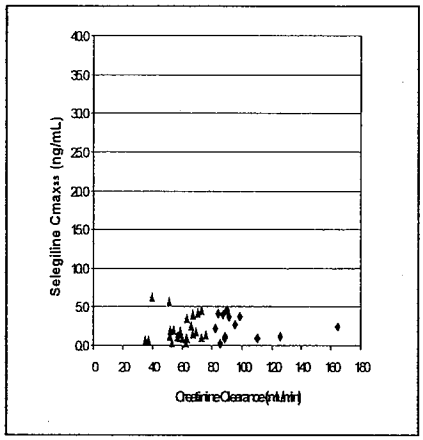
- Selegiline transdermal patch (STS; 18mg/10 cm^2) single application in elderly patients (mean age 70 years), led to an at least 40-fold increased AUC_{0-24} compared to a single dose Eldepryl® 10 mg without unusual side effects.

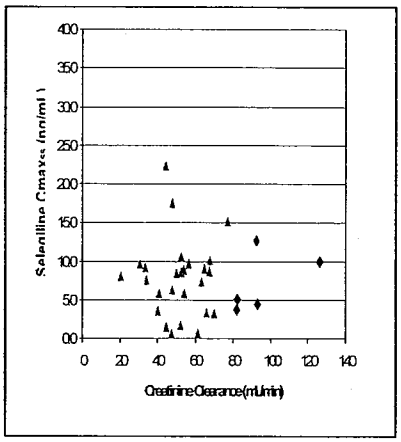
Reviewer's Comment:

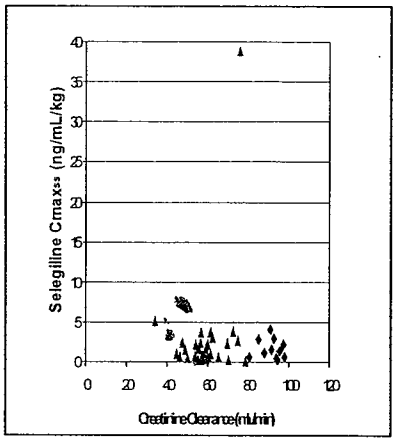
Reference for this statement is not provided. Looking at the label of EMSAM, transdermal patch for selegiline (N21-336), Study P9809 showed that after single application of STS 20mg/20 cm^2 ,the AUC was 46 ng. h/ml. With Eldepryl 10 mg the AUC0-t was 4.5 ng.h/ml The exposure from STS is only 10 fold higher than those seen with Eldepryl 10 mg given as single dose. The side effect from the transdermal patches can be assessed by the Medical Officer. The transdermal patch was approved by FDA in February 2006.

- No correlation was observed between the apparent creatinine clearance (ranging from normal function to moderate dysfunction), Zelapar™ dose and selegiline $Cmax_{ss}$ in the supportive clinical study Z/SEL/95/008. Additionally, there was no relationship between apparent creatinine clearance and discontinuations either within or across groups.

Figure: Creatinine Clearance versus renal function:







Zelapar™ 1.25 mg QD
▲renal dysfunction mild to moderate
◆ normal renal function

Zelapar™ 10 mg QD
▲renal dysfunction mild to severe
◆ normal renal function

Eldepryl® 10 mg QD
▲renal dysfunction mild to moderate
◆ normal renal function

Reviewer's Comment:

Raw data for these figures were not provided by the sponsor, but was made available upon request. Study Z/SEL/95/008 has no subjects with severe impairment in the Zelapar 1.25 mg dose group, the eldepryl dose group and only one subject with severe impairment in the Zelapar 10 mg dose group. From the data there is no relationship between the cmax value and mild to moderate impairment of subjects.

- A combined population pharmacokinetic analysis of Z/SEL/97/025 and Z/SEL/97/026 reported the median AUC values of 3.33 and 6.66 ng.h/mL for 1.25 mg/day and 2.5 mg/day Zelapar™, and did not report any correlation between selegiline clearance and serum creatinine concentration. As was the case for Study Z/SEL/95/008, there was no relationship between creatinine clearance, Cmax and adverse events or discontinuations.

Reviewer's Comment:

In the original NDA, the sponsor themselves considered this population analysis unreliable, as samples were limited to Cmins and in some cases were more than 18 hours after dosing. The sponsor mentions that there was no relationship between creatinine clearance, Cmax and adverse events or discontinuations based on this analysis as was in the case of Study Z/SEL/95/008. However, from this analysis no Cmax's were obtained. No definitive conclusions can be drawn from this analysis.

- The sponsor has provided additional rationale on safety of selegiline from literature and post marketing database. This should be assessed by the Medical Officer.

<u>Overall conclusions from ISSUE 5:</u>

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 t1/2, which adds on to the difficulty of interpreting the PK data.

Therefore, the subjects with the highest Cmax 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 supratherapeutic 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.

ISSUE 6: Discrepancy of food effect of zydis selegiline and that previously known of selegiline

Discrepancy on Eldepryl Food effect:

Current Zydis selegiline NDA:	Food decreases exposure by 1.4-3.8-fold both with zydis and Eldepryl formulations.
Eldepryl original NDA:	Food increases exposure by 3-fold

The sponsor proposes that the discrepancy in food effect on eldepryl between the conclusions of the food effect study with zydis selegiline and that previous known for eldepryl is due to different doses and dosing regimens (single dose in the morning [Z/SEL/96/008] vs. the additive morning and noon doses [Barrett Study or Eldepryl NDA information] and differing meal compositions [both studies using the 'FDA breakfast', but the Barrett study had an additional undefined 'clinical lunch' administered after the second dose]).

In study Z/SEL/96/008, an open-label, randomized four-period crossover design study, twelve volunteers received either a single 5 mg Zydis selegiline tablet (investigational tablet formulation) or two 5 mg Eldepryl® tablets following a high-fat (FDA) breakfast or in fasted state. Plasma levels of selegiline at 0, 5, 10, 15 30, 45 minutes and 1, 1.5, 2, 3, 4, 5 6, 12 and 24 hours were determined by LC-MS/MS methodology. Mean pharmacokinetic parameters for selegiline obtained are summarized as follows:

Table 1: Effect of Food on the Pharmacokinetics of Selegiline Administered as Either Zelapar™ (Zydis Selegiline) or Eldepryl® –Study Z/SEL/96/008

Drug	Treatment	$AUC_{(0-\infty)}$ (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
Zelapar™ (one 5 mg Tablet)	Fasted	5.829	7.804	0.208
	Fed	3.710	4.490	0.202
	Fed/Fasted	0.64	0.58	0.97
Eldepryl® Tablet 10 mg (two 5 mg Tablets)	Fasted	3.584	3.093	0.688
	Fed	2.382	1.416	1.604
	Fed/Fasted	0.66	0.46	2.33

Results of the study indicate that co-administration of Zydis selegiline with a high-fat breakfast yielded an AUC and a C_{max} for selegiline that were 64% and 58% respectively, of those obtained in the fasted state.

Similarly, co-administration of Eldepryl® with a high-fat breakfast yielded a C_{max} and an AUC for selegiline that were 66% and 46% respectively, of those obtained in fasted state. (i.e. decrease in exposure under fed conditions for both the zydis and Eldepryl formulations).

These results seem to be different from those reported previously by Barrett el al (1996) for Eldepryl® in which there is increased exposure under fed conditions. In a randomized, two-way crossover study, 14 male volunteers were administered a 5 mg Eldepryl® dose at both 8 AM and 12 noon while fasting or

immediately after a high fat (FDA) breakfast and a "standard" clinic lunch (no detail on the content of this meal). Plasma levels at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 4, 4.33, 4.67, 5, 5.33, 5.67, 8, 12, 24, 36, 48, and 72 hours were determined by LC-MS/MS methodology. Mean pharmacokinetic parameters are reported for selegiline in the following Table.

Table 2: Effect of Food on the Pharmacokinetics of Selegiline Administered as Eldepryl® (5 mg tablet BID) – Barrett Study

Treatment	$AUC_{(24h)}$ (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
Fasted	0.56	0.32	4.6	1.51
Fed	2.27	1.05	3.6	1.52
Fed/Fasted	4.05	3.28	0.78	1.01

Based on these data, it was concluded by the authors that the bioavailability of selegiline is increased 3 to 4 fold when it is taken with food. This conclusion is different from the sponsor's results with the study conducted in the development program for zydis selegiline as shown in Table 1. The differences between the two studies that the sponsor thinks can explain these results:

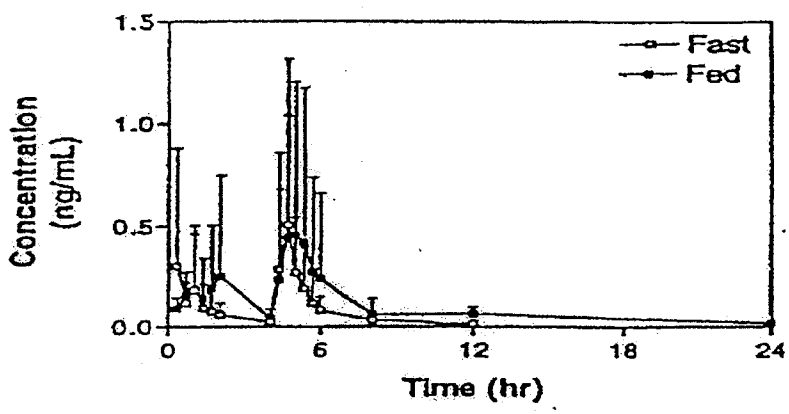
(a) Dosing was 5 mg BID (5 mg given at 8AM and 5 mg at noon) in the Barrett study for oral selegiline as compared to a single 10 mg morning dose in the sponsor's study.

(b) For the fed treatment group, a high fat breakfast (FDA) was given in the morning for both studies, however a "standard" clinic lunch (not defined) was given in the Barrett study.

(c) $AUC_{(0-\infty)}$ for a single 10 mg oral selegiline dose was determined in the sponsor's study, while $AUC_{(0-24h)}$ was calculated after the selegiline 5 mg BID in the Barrett study.

Mean plasma levels of selegiline in the Barrett el al (1996) study are illustrated in Figure 1.

Figure 1. Selegiline plasma concentration fasted and fed (Barrett el al (1996))



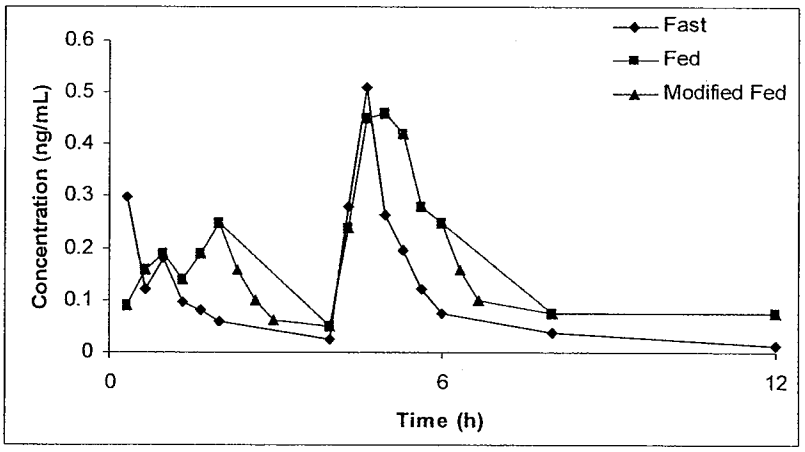
No plasma samples were collected between 2 and 4 hours and between 6 and 8 hours, rather the AUC was estimated by drawing a straight line between 2 and 4 hours and between 6 and 8 hours. According to the sponsor, this approach overestimates the AUC for the fed treatment to much greater extent than for fasted treatment. To correct this, the sponsor estimated (modified) plasma levels for fed treatment at 2.33, 2.67, 3, 6.33 and 6.67 hours based on the $t_{1/2}$ obtained with fed treatment between 5 and 6 hours. Plasma levels including actual values and estimated values were as follows:

Table 3. Reported and estimated Selegiline Plasma Concentration – Barrett Study

Time (hr)	Selegiline Concentration (ng/mL)		
	Fast	Fed	Fed (modified)
0.33	0.3	0.09	0.09
0.67	0.12	0.16	0.16
1.00	0.18	0.19	0.19
1.33	0.095	0.14	0.14
1.67	0.08	0.19	0.19
2.00	0.06	0.25	0.25
2.33	-	-	0.157
2.67	-	-	0.099
3.00	-	-	0.062
4.00	0.025	0.05	0.05
4.33	0.28	0.24	0.24
4.67	0.51	0.45	0.45
5.00	0.265	0.46	0.46
5.33	0.195	0.42	0.42
5.67	0.12	0.28	0.28
6.00	0.075	0.25	0.25
6.33	-	-	0.157
6.67	-	-	0.099
8.00	0.0375	0.075	0.075
12.00	0.0125	0.075	0.075

Figure 2 illustrates the selegiline plasma levels for fasted, fed and fed modified.

Figure 2: Selegiline plasma concentration-time profiles (Reported and estimated from Barrett el al (1996)



Based on these plasma levels, pharmacokinetic parameters were calculated and are presented in Table 14.

Table 4. Reported and estimated Selegiline PK Parameters Fasted vs. Fed – Barrett Study

Treatment	First (morning) Dose			Second Dose		
	Tmax (h)	Cmax (ng/mL)	AUC(0-4h) (ng.h/mL)	Tmax (h)	Cmax (ng/mL)	AUC(0-4h) (ng.h/mL)

Fast	0.33	0.30	0.35	4.67	0.51	0.74
Fed	2.00	0.25	0.60	5.00	0.46	1.39
Fed (modified)	2.00	0.25	0.49	5.00	0.46	1.29
Fed/Fast	6.06	0.83	1.71	1.07	0.90	1.88
Fed (modified)/Fast	6.06	0.83	1.40	1.07	0.90	1.74

For the morning dose, C_{max} in fed treatment was 83% of that obtained in the fasted treatment. This is in good agreement with data from our study that a high fat breakfast yielded a C_{max} which was 64 % of that obtained in fasted state. Based on the modified plasma levels, the AUC in fed treatment was higher (40%) compared to the fasted treatment group. In summary, based on the evidence stated above, the sponsor believes that the Barrett's study corroborates our study when the studies are examined more closely and comparisons only examine the morning dose.

In the Barrett et al (1996) study, volunteers in the 'fed group', in addition to a high fat (FDA) breakfast, also received a "clinical lunch" at 12:00 noon. The authors reported the effects of the "clinical lunch" on the AUC ratios of metabolites to selegiline as follows:

Table 5. Reported Metabolic Ratios Fasted vs. Fed – Barrett Study

Treatment	Desmethylselegiline	Methamphetamine	Amphetamine
Fasted	109.4	841.4	290.3
Fed	51.3	328.4	111.9
Fed/Fasted	0.47	0.39	0.39

According to the sponsor it is clear that the "clinical lunch" decreased the AUC ratios strongly indicating that the "clinical lunch" may contain component(s) (such as grape fruit juice) which strongly inhibited the metabolism of selegiline to these metabolites. Therefore, the conclusion of this segment of the food effect study is questionable.

In summary, based upon the evidence stated above, the sponsor believes that the Barrett study actually corroborates their 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.

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 selelgiline 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 Cmax's 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.

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/s/

Veneeta Tandon
5/15/2006 02:52:58 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/15/2006 06:04:15 PM
BIOPHARMACEUTICS

Mehul Mehta
5/16/2006 11:07:37 AM
BIOPHARMACEUTICS

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Clinical Pharmacology/Biopharmaceutics Review
Type A meeting for Complete Response to AE letter

PRODUCT (Generic Name):	ZYDIS® Selegiline HCl
PRODUCT (Brand Name):	ZELAPAR ODT
DOSAGE FORM:	Orally Disintegrating Tablets (ODT)
DOSAGE STRENGTHS:	1.25 mg
NDA:	21-479
INDICATION:	Adjunct treatment for the management of Parkinson's disease in patients who are exhibiting deterioration of response to levodopa/carbidopa therapy
NDA TYPE:	Type A meeting for Complete response to AE letter
SUBMISSION DATE:	10/21/05
MEETING DATE:	11/8/05
SPONSOR:	Valeant Pharmaceuticals International.
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DCPB I, HFD 860
OND DIVISION:	HFD 120

BACKGROUND 2
RECOMMENDATIONS 3

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BACKGROUND

In this submission the sponsor seeks Agency advice on the main issues raised in the approvable letter dated September 2005 and their approach to respond to the issues in the complete response to the approvable letter submission.

The main issues were:

- Renal and hepatic impairment studies to be conducted Phase IV instead of prior approval: Regarding this issue the sponsor was asked to provide additional information on the status of liver impairment in the patients used in the Antilla literature article. The sponsor plans to request this from the first author. Decision whether these studies can be done post approval as opposed to prior approval as initially requested will be made at that time, during the review.

- Discrepancy of the food effect study conducted by the sponsor and that in the original oral NDA study: The sponsor proposes to explain this discrepancy based on the first dose of oral selegiline that was taken after a high fat meal. The second dose of oral selegiline (Eldepryl) was taken 4 hours apart after a 'clinical lunch'. Graphical comparisons were shown of the data.

- Metabolism of selegiline: The sponsor has provided additional literature articles on the metabolism of selegiline. Based on these literature articles, the sponsor concludes that CYP 1A2 and CYP 3A4 are the major enzymes, while CYP2B6, CYP2C19 and CYP2D6 play a minor role in selegiline's metabolism. In spite of the additional information provided, the overall picture of the metabolic pathway is still confusing.

  The following are the conclusions of the various authors regarding the involvement of the major and minor CYP isoenzymes. These authors have either used hepatic microsomes with specific inhibitors, correlation study or recombinant assay to determine the metabolic pathway of selegiline. In all in in vitro studies, the concentrations of the inhibitors used are much higher than their Ki's. The results of the in vitro liver microsome study using specific inhibitors do not give the same results as the recombinant assay.

  - Taavitsainen et. al (2000): CYP 1 A2 and CYP 3A4 -----major
CYP 2C19 and CYP 2D6-----not involved
  - Salonen et al (2003): CYP 1A2 and CYP 2B6------major
CYP 2C19 and CYP 2C8, CYP 3A4-----minor
CYP 2D6-----not involved
  - Wacher et. al (1996): CYP 3A4 -----major
CYP 1 A2 and CYP 2D6 -----minor
  - Kivistro et. al CYP 3A4----not involved based on an itraconazole study
  - Hidestrad et. al (2001): CYP 2C19 and CYP 2B6------major
CYP 1 A2 and CYP 3A4 -----minor
CYP 2D6-----not involved
  - Laine et. al (2001) CYP 2D6-----not involved based 2C19 polymorphism not being involved

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/s/

Veneeta Tandon
1/5/2006 01:37:40 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
1/5/2006 01:54:28 PM
BIOPHARMACEUTICS

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Clinical Pharmacology/Biopharmaceutics Review Addendum to the Review of the Response to the AE Letter

PRODUCT (Generic Name):	ZYDIS® Selegiline HCl
PRODUCT (Brand Name):	ZELAPAR ODT
DOSAGE FORM:	Orally Disintegrating Tablets (ODT)
DOSAGE STRENGTHS:	1.25 mg
NDA:	21-479
INDICATION:	Adjunct treatment for the management of Parkinson's disease in patients who are exhibiting deterioration of response to levodopa/carbidopa therapy
NDA TYPE:	Complete response to AE letter
SUBMISSION DATE:	3/31/05 5/27/05 8/3/05 8/4/05
SPONSOR:	Valeant Pharmaceuticals International.
REVIEWER:	Andre Jackson
TEAM LEADER:	Raman Baweja, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

1.DRUG METABOLISM:

DRUG METABOLISM REFERENCE 1

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ISSN 0901-9928

Selegiline Metabolism and Cytochrome P450 Enzymes: *In vitro* Study in Human Liver Microsomes*

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(Received October 12, 1999; Accepted January 6, 2000)

The manuscript investigated the metabolism of selegiline in Human liver microsomes. The liver samples were from kidney transplant donors and standard microsomes were prepared in pH 7.4 phosphate buffer . The authors used UV-HPLC to analyze for selegiline and its metabolites. There were also CYP –isoform specific assays for the different enzymes.

They investigated:

1. the metabolism of selegiline in vitro
2. inhibition of selegiline by CYP inhibitors
3. inhibition of oxidative selegiline metabolism by furafylline(CYP1A2)
4. inhibition of oxidative selegiline metabolism by fluvoxamine(CYP2C9)
5. inhibition of CYP specific model reactions by selegiline, desmethylselegiline and l-methamphetamine
6. effect of selegiline on d-mephenytoin 4'hydroxylation(CYP2C19)
7. effect of selegiline on ethoxyresorufin O-dethylation(CYP1A2)

RESULTS

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Table 1.

Kinetics of inhibition by selegiline and some reference inhibitors on ethoxyresorufin O-deethylase and s-mephenytoin 4'-hydroxylase activities and on desmethylselegiline (DMS) and l-methamphetamine (MAP) formation.

Enzyme/reaction	App. K_m (μM)	App. V_{max} (pmol/min/mg)	Inhibitor	App. K_i (μM)	Inhibition type
DMS formation (selegiline N-demethylation)	149	243	furafylline	1.7	mixed
			ketoconazole	15	mixed
			fluvoxamine	9	mixed
MAP formation (selegiline N-depropargylation)	293	1351	furafylline	–	
			ketoconazole	18	mixed
			fluvoxamine	25	mixed
Ethoxyresorufin O-deethylase	0.13	75	selegiline	96	competitive
Mephenytoin 4'-hydroxylase	11	74	selegiline	7	mixed

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The results show that based upon the Ki values that only the index compound furafylline was likely to inhibit DMS formation which would indicate a CYP1A2 reaction for the metabolism of selegiline.

Based upon the guidance method of assessing the clinical relevance of competitive CYP inhibition (i.e., I/Ki) a calculation was made using the firm's estimate of Cmax. The calculation defines Cmax as I (where I=Cmax=0.029uM from the firm in volume 2 D2 page 1) and the apparent Ki value from Table 1 results in a I/Ki <<<0.1 which means that selegiline is highly unlikely to inhibit CYP1A2.

Table 2.

Potencies of CYP isoform specific reference inhibitors on desmethylselegiline (DMS) and l-methamphetamine (MAP) formation from selegiline in human liver microsomes.

CYP inhibited	Reference inhibitor	DMS formation IC_{50} (μM)	MAP formation IC_{50} (μM)
CYP1A2	furafylline	0.45	>1000
	fluvoxamine*	35	14.5
		1.7	2.1
CYP2A6	methoxsalen	31	390
	coumarin	>1000	>1000
CYP2C9	sulphaphenazole	>1000	>1000
CYP2C19	omeprazole	>1000	>1000
	rac-mephenytoin	>1000	>1000
CYP2D6	quinidine	>100	>100
CYP2E1	pyridine	>1000	>1000
CYP3A4	ketoconazole**	53	32
		32	24

* Fluvoxamine inhibits also CYP2C19 and CYP3A4. Two different liver samples were used.
** Ketoconazole as an inhibitor: selegiline concentration was 250 μM. In other assays, selegiline concentration was 100 μM. Two different liver samples were used.

Table 2 lists the CYP specific reference inhibitors to determine which pathways are most important. The IC50 values would indicate that mainly CYP1A2 and CYP3A4 are the most important enzymes in the metabolism of selegiline.

Table 3.

Potencies for selegiline, desmethylselegiline (DMS), l-methamphetamine (MAP) and reference inhibitors on CYP isoform specific model reactions in human liver microsomes.

CYP inhibited (substrate in the reaction)	Selegiline IC_{50} (μM)	DMS IC_{50} (μM)	MAP IC_{50} (μM)	Reference inhibitor IC_{50}(μM)
CYP1A2 (1 μM ethoxyresorufin)	350	409	>1000	0.45 (furafylline)
CYP2A6 (10 μM coumarin)	580	>1000	>1000	0.7 (methoxsalen)
CYP2C9 (1 mM tolbutamide)	670	>1000	>1000	4.1 (sulphaphenazole)
CYP2C19* (100 μM *rac*-mephenytoin)	21	26	>1000	67 (omeprazole)
CYP2D6 (100 μM dextromethorphan)	580	165	414	0.41 (quinidine)
CYP2E1 (100 μM chlorzoxazone)	430	463	>1000	4.7 (pyridine)
CYP3A4 (100 μM testosterone)	825	>1000	~1000	0.34 (ketoconazole)

* An average of determinations with three different human liver microsomal samples. Other values are from the determination with one liver sample.

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The table shows that selegiline, and DMS has the largest affinity for CYP2C19, however because 21 uM and 26 uM represent 700 to 1000 fold increase of what is likely seen in plasma at Cmax, it is highly unlikely to occur.

Conclusions:

- 1.It appears that CYP1A2 and CYP 3A4 are involved in the metabolism of selegiline based upon the in vitro microsome study.
- 2.Selegiline does not seem to inhibit the metabolism of the CYP enzymes.
- 3.There were no studies related to the induction of CYP isoforms in the reference so that remains an area which needs further investigation.

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DRUG METABOLISM REFERENCE 2

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DRUG METABOLISM AND DISPOSITION
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DMD 29:1480–1484, 2001

Vol. 29, No. 11
408/939576
Printed in U.S.A.

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

MATS HIDESTRAND, MIKAEL OSCARSON, JARMO S. SALONEN, LEENA NYMAN, OLAVI PELKONEN, MIIA TURPEINEN, AND MAGNUS INGELMAN-SUNDBERG

The manuscript studied:

1. the metabolism of selegiline using yeast cells that had been encoded with human cytochrome P450 enzymes 1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4. The concentrations of the specific P450's varied.
2. they also used human liver microsomes whose non specific binding was blocked using 5% nonfat dry milk to study CYP2B6 involvement. The CYP2B6 was blocked by using mouse monoclonal inhibitory antibodies.

RESULTS

TABLE 1

V_{max} and K_m values for P450-mediated selegiline metabolism to desmethylselegiline and levomethamphetamine

The subsequent calculation of hepatic clearance uses the conversion factors described under *Materials and Methods*. The contribution of each specific enzyme to the hepatic clearance is also shown. The data for the specific P450 content were from GENTEST (http://www.gentest.com/prod_inserts/H161_2.htm#immunoquantitation).

	Desmethylselegiline					
	CYP Content	K_m	V_{max}	V_{max}/K_m	Hepatic Clearance	Hepatic Clearance
	pmol/mg	*μM*	*pmol/pmol/min*	*ml/μmolP450*min*	*l/h*	*% of total*
1A1	[b]	161	7	43	0	[b]
1A2	50	334	12	36	7	6
2A6	66	376	5	13	3	3
2B6	26	25	52	2055	62	57
2C8[a]	[b]	82	3	37	[b]	[b]
2C9	55	628	3	5	1	1
2C19	26	20	7	350	26	24
2D6	11	[c]	[c]	[c]	[c]	[c]
2E1	53	678	7	10	2	2
3A4[a]	127	608	10	16	8	7

	Levomethamphetamine					
	CYP Content	K_m	V_{max}	V_{max}/K_m	Hepatic Clearance	Hepatic Clearance
	pmol/mg	*μM*	*pmol/pmol/min*	*ml/μmolP450*min*	*l/h*	*% of total*
1A1	[b]	117	10	85	0	[b]
1A2	50	379	32	84	14	9
2A6	66	[c]	[c]	[c]	[c]	[c]
2B6	26	33	65	1994	62	40
2C8[a]	[b]	630	7	11	0	[b]
2C9	55	252	2	8	2	0
2C19	26	20	30	1500	56	36
2D6	11	[c]	[c]	[c]	[c]	[c]
2E1	53	437	6	14	3	2
3A4[a]	127	612	28	46	19	12

[a] Including human cytochrome P450 reductase and cytochrome b_5.
[b] P450 content not provided.
[c] Below the limit of detection.

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Table 1 shows that based upon the Km values that 2B6 and 2C19 were the major enzymes involved in the metabolism of selegiline(81% and 76%) respectively. They seem to account for most of the transformation while CYP 3A4 and 1A2 are minor(6-12%).

TABLE 2

Inhibition of selegiline metabolite formation in human liver microsomes using mouse monoclonal inhibitory antibodies against human CYP2B6

Liver	Substrate Conc.	% Inhibition by CYP2B6 Antiserum	
		Levomethamphetamine	Desmethylselegiline
	μM		
HL33	25	43.2	40.2
HL33	100	18.2	19.5
HL44	25	25.1	7.4
HL44	100	23.0	20.4
HL41	25	2.3	−28.6

Table 2 shows that the preparations with the highest CYP2B6 content as determined by Western blot HL33 and HL44. HL 41 had a low CYP2B6 content. The results show the greatest inhibition in the microsomal preparations with the highest concentrations of CYP2B6.

Conclusions:

- 1.CYP2C19 and CYP2B6 seem to be involved in selegiline metabolism

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DRUG METABOLISM REFERENCE 3

Eur J Clin Pharmacol (2001) 57: 137–142
DOI 10.1007/s002280100289

PHARMACOKINETICS AND DISPOSITION

Kari Laine · Markku Anttila · Leena Nyman
Anneli Wahlberg · Leif Bertilsson

CYP2C19 polymorphism is not important for the in vivo metabolism of selegiline

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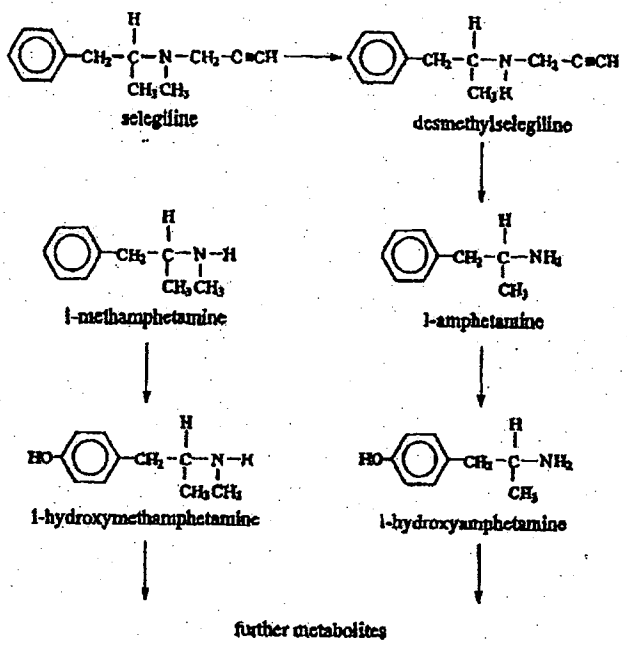
Fig. 1 Metabolic pathways of selegiline in humans



The article studied the metabolism of selegiline in 6 extensive and six poor metabolizers. Demographic characteristics were:

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Table 1 Demographic characteristics of the subjects. For both groups data are given as mean values and range for six subjects

	Poor metabolisers	Extensive metabolisers
Sex (M/F)	1/5	5/1
Age (years)	29 (24–37)	26 (20–36)
Weight (kg)	70 (56–98)	72 (60–93)
Mephenytoin S/R ratio	1.15 (0.99–1.56)	0.12 (0.05–0.25)
CYP2C19 genotype:		
*1/*1	–	4
*1/*2	1	2
*2/*2	5	–

Subjects were phenotyped and genotyped for CYP2C19. The study was a parallel design and studied a single 10 mg dose of selegiline following an overnight fast. Sampling was done for 48 hrs post-dose.

Table 2 Pharmacokinetic parameters of selegiline, desmethylselegiline and l-methamphetamine in extensive (*EM*) and poor (*PM*) hydroxylators of S-mephenytoin after ingestion of a single 10-mg dose of selegiline hydrochloride. Data are given as mean values ± SD for six EM and six PM; time to peak (t_{max}) is given as median with range; AUC ratio was calculated as AUC (metabolite)/AUC(selegiline). (C_{max} peak concentration in serum, $t_{1/2}$ half-life, CL/F estimate of the apparent oral clearance)

Parameter	EM	PM	Percentage difference (PM vs EM)	*P* value
Selegiline				
AUC (ng ml^{-1}•h)	0.72±0.64	1.17±0.67	63%	0.21
C_{max} (ng ml^{-1})	1.14±0.98	1.27±0.90	11%	0.68
t_{max} (h)	0.75 (0.5–1.5)	1.5 (0.5–2)	–	0.51
CL/F (l h^{-1} kg^{-1})	352±293	202±160	–43%	0.30
Desmethylselegiline				
AUC (ng ml^{-1}•h)	41±11	69±11	68%	0.0017
C_{max} (ng ml^{-1})	22±4.0	26±8.2	21%	0.33
t_{max} (h)	1 (0.5–1.5)	1 (1–2.5)	–	0.23
$t_{1/2}$ (h)	2.6±1.2	4.3±2.7	65%	0.14
AUC ratio	88±50	90±67	2%	0.90
l-methamphetamine				
AUC (ng ml^{-1}•h)	249±49	196±66	–21%	0.15
C_{max} (ng ml^{-1})	11.6±1.7	10.6±6.4	–9%	0.39
t_{max} (h)	3 (1.5–5)	4 (1.5–4)	–	0.47
$t_{1/2}$ (h)	12.7±2.1	12.4±4.1	–2%	0.75
AUC ratio	599±477	289±270	–52%	0.14

Mean AUC was 63% higher in PM subjects compared to EM's. Desmethylselegiline levels were 68% higher in PM's than EM's. Lmethamphetamine levels were slightly lower in PM's than in EM's. The authors conclude that one would expect a several fold difference if metabolism status mattered.

Conclusion:

- 1.Based upon the small N and the great deal of variability up to 100% CV it would be difficult to be certain of these results. However the overall trend for the means show no large differences.

- 2.Since the authors did not investigate other inhibitors their conclusion related to the importance of CYP2C19 in selegiline metabolism would need additional supporting information from the sponsor.

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DRUG METABOLISM REFERENCE 4

Eur J Clin Pharmacol (2001) 57: 37–42
DOI 10.1007/s002280100278

PHARMACOKINETICS AND DISPOSITION

Kari T. Kivistö · Jun-Sheng Wang · Janne T. Backman
Leena Nyman · Päivi Taavitsainen · Markku Anttila
Pertti J. Neuvonen

Selegiline pharmacokinetics are unaffected by the CYP3A4 inhibitor itraconazole

Received: 13 September 2000 / Accepted in revised form: 1 February 2001 / Published online: 28 March 2001
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The authors studied the pharmacokinetics of selegiline in 12 healthy non-smokers 20-32 yrs old. Females using oral contraceptives were not included. A randomized placebo-controlled crossover study with two phases was used. The dose of itraconazole was 200 mg daily for 4 days. The maximum recommended dose is 400 mg. On day 4 subjects were given selegiline on an empty stomach. In vitro studies were also done using human liver microsomes harvested from a single male subject.

Table 1 The pharmacokinetic variables of selegiline, desmethylselegiline and *l*-methamphetamine in 12 healthy subjects after 10 mg oral selegiline hydrochloride, following intake of 200 mg itraconazole or placebo once daily for 4 days. Data are mean ± SD; time to peak concentration (t_{max}) values are given as median with (range). (C_{max} Peak serum concentration, $t_{1/2}$ elimination half-life, $AUC_{0-6\,h}$ area under the serum concentration–time curve from 0 to 6 h)

Variable	Placebo phase (control)	Itraconazole phase	Mean difference between itraconazole and placebo (95% CI)
Selegiline			
C_{max} (ng ml^{-1})	0.65 ± 0.53	0.58 ± 0.41	−0.08 (−0.35, 0.20) 12%
t_{max} (h)	1 (0.5–1)	1 (0.5–1)	
$AUC_{0-6\,h}$ (ng ml^{-1} h)	1.0 ± 1.4	0.87 ± 1.04	−0.18 (−0.65, 0.29) 13%
Desmethylselegiline			
C_{max} (ng ml^{-1})	15.4 ± 4.1	16.2 ± 4.3	0.84 (−1.04, 2.72) 4%
t_{max} (h)	1 (0.5–1.5)	1 (0.5–1.5)	
$t_{1/2}$ (h)	1.3 ± 0.5	1.8 ± 1.0	0.5 (−0.1, 1.0)
AUC (ng ml^{-1} h)	36.1 ± 14.2	39.9 ± 15.8*	3.8 (0.1, 7.4) 10%
l-Methamphetamine			
C_{max} (ng ml^{-1})	10.7 ± 2.8	11.1 ± 4.4	0.4 (−1.3, 2.2) 3.7%
t_{max} (h)	4 (2–6)	5 (2–10)	
$t_{1/2}$ (h)	16.8 ± 4.2	16.3 ± 5.6	−0.5 (−3.8, 2.8)
AUC (ng ml^{-1} h)	281 ± 115	277 ± 134	−4 (−63, 55) 1.4%

*$P < 0.05$; significantly different from the placebo phase

Itraconazole showed no significant effects on the pharmacokinetics of selegiline or its metabolites. This was also supported by the in vitro study with itraconazole levels of

0.01-100uM which are well below the 0.27 uM value in the guidance but far exceeds the upper Ki value of 2.3 uM listed in the guidance.

Conclusion:

These results are at odds with those from Taavitsainen et al , but based upon study design and levels studied one can not easily explain the discrepancy and further investigation is warranted.

Overall Conclusion:

- 1.The nature and types of studies done in the literature are contradictory for example Taavitsainen et al implicates CYP1A2 and CYP3A4 in the metabolism of selegiline.

- 2. Hidestrand et. al. report based upon in vitro work that CYP2B6 and CYP2C19 are major contributors while CYP3A4 and 1A2 are minor players of the in vitro metabolism.

- 3. Both Taavitsainen et. al. and Hidestrand et. al. studied the full range of isozymes from 1A2 to 2E1.

- 4.The firm needs to repeat these in vitro studies paying close attention to CYP1A2, CYP3A4, CYP2B6 and CYP2C19 with full scale inhibition studies. Further the ability of selegiline to induce these enzymes needs further study.

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2. ORAL CONTRACEPTIVES for Companion NDA19-334 :

OC REFERENCE 1

Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids

Kari Laine,[1] Markku Anttila,[2] Antti Helminen,[1] Hari Karnani[2] & Risto Huupponen[1]
[1]*Department of Pharmacology and Clinical Pharmacology, University of Turku, Turku and* [2]*Orion Corporation, Orion Pharma, Turku, Finland*

Eight female subjects (aged between 20 and 27 years and weighing between 56 and 75 kg) participated in the study. All the subjects were nonsmokers and with the exception of four subjects, who took oral contraceptives (three subjects used the combination of gestodene 75 (ug/ethinylestradiol 30 ug and one subject a triphasic preparation containing levonorgestrel 50-125 (ug/ethinylestradiol 30-40 ug, none of the subjects was taking any prescribed or nonprescribed drugs for 2 weeks before or during the study. The demographic characteristics of the subjects using oral contraceptives did not differ from those not receiving any concomitant medications.

The subjects received a single dose of 5 mg (one Eldepryl, 5 mg tablet, 10 mg (two tablets), 20 mg (four tablets) or 40 mg (eight tablets) of selegiline hydrochloride in an open 4-period randomized study with a washout period of at least 2 weeks between the phases. The selegiline dose was ingested on an empty stomach (after an overnight fast) with 200 mL of water. Fasting was continued for 3 h after drug ingestion. Use of food containing large amounts of tyramine was restricted within 1 week before and 2 weeks after the study drug administration. Alcohol intake was forbidden for 2 days before and 24 h after selegiline administration.

Blood samples (10 mL) were drawn through an ante-cubital venous cannula at 0, 15, 30 and 45 min and 1, 1.5, 2, 2.5, 3, 4 and 5 h after drug ingestion. The blood samples were centrifuged and serum was separated for the analysis of selegiline and desmethylselegiline concentrations.

Table 1 Pharmacokinetic parameters of selegiline and desmethylselegiline after oral administration of 5, 10, 20 or 40 mg selegiline HCl to healthy volunteers with no concomitant medication ($n=4$) and with concomitant oral steroids ($n=4$).

Parameter	*No concomitant medication*				*Concomitant oral steroids*			
	5 mg	*10 mg*	*20 mg*	*40 mg*	*5 mg*	*10 mg*	*20 mg*	*40 mg*
Selegiline								
AUC (ng ml^{-1} h)	0.04 (0.04–0.08)	0.5 (0.3–0.7)	0.9 (0.5–2.1)	5.3 (3.4–6.5)	1.8 (0.6–5.3)†	11 (1.5–13)*	22 (16–51)†	89 (51–179)†
95% CI for ratio of means					(11, 131)	(3.6, 54)	(9.7, 70)	(7.5, 42)
C_{max} (ng ml^{-1})	0.05 (0.05–0.2)	0.8 (0.5–1.1)	1.0 (0.6–2.0)	5.4 (1.6–11)	2.8 (1.3–7.5)†	8.9 (2.7–22)*	15 (8.1–44)†	101 (12–203)*
95% CI for ratio of means					(10, 148)	(3.6, 34)	(5.2, 51)	(1.7, 118)
t_{max} (h)	0.75 (0.75–0.75)	0.75 (0.5–1.5)	0.75 (0.5–0.75)	1.3 (0.5–3.0)	0.5 (0.5–0.75)	0.5 (0.5–0.75)	0.5 (0.5–2.5)	0.5 (0.5–0.75)
$t_{1/2}$ (h)	n.a.	n.a.	n.a.	n.a.	n.a.	1.8 (1.5–4.3)[a]	1.4 (1.0–1.9)[a]	1.6 (1.5–2.1)
Desmethylselegiline								
AUC (ng ml^{-1} h)	12 (5.9–18)	31 (23–41)	63 (50–98)	115 (102–151)	18 (12–32)	33 (26–86)	102 (64–138)	269 (178–379)
95% CI for ratio of means					(0.8, 3.6)	(0.6, 2.6)	(0.8, 2.8)	(0.6, 2.9)
C_{max} (ng ml^{-1})	8.6 (2.7–11)	21 (15–27)	39 (27–50)	64 (24–73)	9.4 (7.3–16)	14 (8.5–57)	29 (24–80)	64 (53–114)
95% CI for ratio of means					(0.6, 3.6)	(0.3, 2.5)	(0.5, 1.9)	(0.5, 3.6)
t_{max} (h)	0.75 (0.5–1.0)	0.63 (0.5–1.0)	0.75 (0.5–2.0)	0.88 (0.75–3.0)	0.75 (0.5–1.0)	0.5 (0.5–0.75)	0.75 (0.75–3.0)	0.88 (0.5–2.5)
$t_{1/2}$ (h)	1.4 (1.2–2.7)	1.6 (1.3–1.8)	1.7 (1.6–1.9)	1.5 (1.3–1.7)	1.9 (1.3–3.4)	1.9 (1.8–3.0)	2.1 (1.7–3.0)	2.8 (2.5–5.0)*
95% CI for ratio of means					(0.6, 2.5)	(0.9, 1.9)	(0.9, 1.8)	(1.4, 3.1)

All data are given as median (range); n.a., not assessable; [a]$n=3$; CI, confidence interval. Statistically significant difference compared with the no-concomitant-medication group, *$P<0.05$; †$P<0.001$.

Cycle

The table shows that in the presence of OC's the total AUC and Cmax for selegiline were 10-20 fold higher. The high levels of the desmethylselegiline (i.e., compared to no concomitant medication) is somewhat unexpected although one of the alternate pathways may show the expected lower levels if in fact the drug's metabolism is inhibited. There should be mass balance for the metabolites. If the parent increases there should be less overall metabolism.

Conclusion:

- Selegiline levels increase 10-20 fold for subjects taking gestodene 75 (ug/ethinylestradiol 30 ug)and the triphasic preparation levonorgestrel 50-125 (ug/ethinylestradiol 30-40 ug).

- The author points out that OC's in Parkinson patients may not be a concern but since levonorgestrel is used for Hormone Replacement Therapy in postmenopausal women the findings may have clinical relevance.

- The following was excerpted from the PDR:

Ethinyl estradiol: Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of Cytochrome P450 (CYP3A) vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation.

Therefore based upon the PDR CYP3A4 is the enzyme of importance for the metabolism of EE. Taavitsainen et al has supported the importance of this enzyme based upon in vitro work while in an vivo study by Kivisto concludes that it is not important in the metabolism of selegiline.

- To further complicate the matter a recent article :

Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs. Zhou S, Yung Chan S, Cher Goh B, Chan E, Duan W, Huang M, McLeod HL. Clin Pharmacokinet. 2005;44(3):279-304
states "Clinically important mechanism-based CYP3A4 inhibitors include antibacterials (e.g. clarithromycin, erythromycin and isoniazid), anticancer agents (e.g. tamoxifen and irinotecan), anti-HIV agents (e.g. ritonavir and delavirdine), antihypertensives (e.g. dihydralazine, verapamil and diltiazem), sex steroids and their receptor modulators (e.g. gestodene and raloxifene), and several herbal constituents (e.g. bergamottin and glabridin)." The article states that gestodene inhibits CYP3A4 which would support its importance in the metabolism of selegiline. Therefore the sponsor needs to obtain additional data to clarify the current conflicting data.

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OC REFERENCE 2

Eur J Clin Pharmacol (2002) 58: 259–263
DOI 10.1007/s00228-002-0469-y

PHARMACOKINETICS AND DISPOSITION

Sanna Palovaara · Markku Anttila
Leena Nyman · Kari Laine

Effect of concomitant hormone replacement therapy containing estradiol and levonorgestrel on the pharmacokinetics of selegiline

Received: 31 October 2001 / Accepted in revised form: 7 March 2002 / Published online: 22 May 2002
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Twelve female volunteers (aged 20-24) participated in this study. The subjects did not smoke or use any concomitant medication during the study. The subjects were at various phases of menstrual cycle, and none had used OCs for at least 2 months before the study.

The study was carried out as a randomised, double-blind, cross-over trial. There was a wash-out period of 4 weeks between the study phases in order to eliminate the carry-over effect and to perform both phases of the study in the same phase of menstrual cycle. In the two phases of the study the subjects took once daily for 10 days either HRT containing 2 mg estradiol valerate and 250 ug levonorgestrel (Cyclabil, Schering, Germany) or matched placebo. The HRT/placebo preparation was taken under the control of the study personnel in the mornings of days 1 and 10; on other days the drugs were self-administered by the subjects between 0800 hours and 1000 hours. On day 10, after fasting overnight, the subjects took a single 10-mg oral dose of selegiline hydrochloride 1 h after ingesting the HRT/placebo. For the determination of selegiline (SEL), desmethylselegiline (OMS) and metamphetamine (MAP) concentrations in serum, venous blood samples (10 mL) were drawn just before and 0.25,0.5,0.75, 1, 1.5,2,2.5,3,4,5,8, 12,24 and 32 h after the ingestion of selegiline from a forearm cannula.

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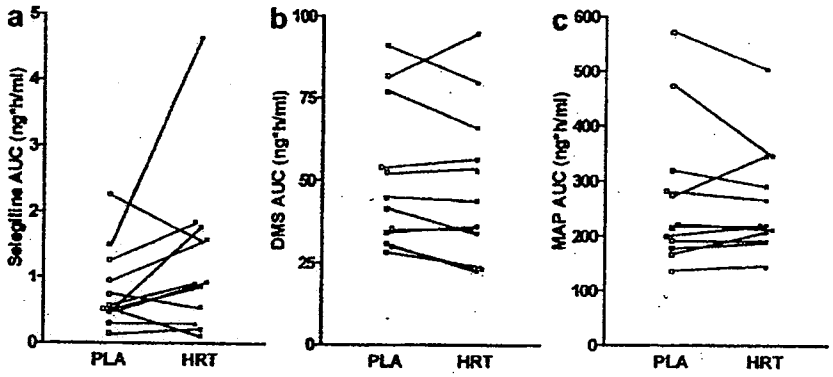
Table 1. Pharmacokinetics of selegiline, desmethylselegiline (DMS) and metamphetamine (MAP) after ingestion of 10 mg of selegiline after 10-day treatment with an hormone-replacement therapy (HRT) preparation or placebo once daily. Data are mean values (SD) for twelve subjects; t_{max} is given as median (range). The pharmacokinetic values are expressed as group means in HRT and placebo phases. *SEL* selegiline, C_{max} maximum serum concentration, t_{max} time to C_{max}, *CL/F* oral clearance, *AUC* area under the serum concentration–time curve, $t_{1/2}$ elimination half-life

Parameter	HRT	Placebo (control)	*P* value for difference
Selegiline			
AUC (ng ml^{-1} h)	1.3±1.2	0.81±0.60	0.14
C_{max} (ng ml^{-1})	1.1±0.90	1.0±0.50	0.54
t_{max} (h)	0.5 (0.5–2)	0.5 (0.5–2)	0.90
CL/F	296±363	294±280	0.99
Desmethylselegiline			
AUC (ng ml^{-1} h)	47±23	50±22	0.07
C_{max} (ng ml^{-1})	17±5.2	21±3.4	0.03
t_{max} (h)	0.75 (0.5–3)	0.75 (0.5–2)	0.19
$t_{1/2}$ (h)	2.3±1.0	2.1±0.9	0.15
Metamphetamine			
AUC (ng ml^{-1} h)	262±98	269±131	0.61
C_{max} (ng ml^{-1})	14±4.3	15±3.8	0.07
t_{max} (h)	2.75 (1–8)	2.8 (2–5)	0.59
$t_{1/2}$ (h)	11±2.5	11±3.7	0.60
AUC ratio			
DMS/SEL	68±61	83±53	0.12
MAP/SEL	607±799	665±1020	0.30

There was a 59% difference (P=0.14, 95% CI -4%, 122%) in the mean AUC of selegiline during the HRT phase compared with the placebo phase (Table I). The Cmax and tmax of selegiline were not changed between the phases (Table I).

Fig. 2. The individual area under the serum concentration–time curve (AUC) values of (a) selegiline, (b) desmethylselegiline (DMS) and (c) metamphetamine (MAP) of 12 healthy subjects after a single 10-mg oral dose of selegiline, following pretreatment with hormone-replacement therapy (HRT) or placebo once daily for 10 days



The individual AUC values for placebo vs HRT subjects shows that for most there was no change for parent, DMS and MAP. However there was one subject that showed a 5 fold increase in selegiline and perhaps was the same subject with decreases in DMS and MAP.

Conclusion:

The data shows that HRT (2mg estradiol valearate/250 ug levonorgestral) did not have any effect on Selegiline, DMS or MAP levels compared to controls.

Overall Conclusions OC/HRT:

Results from the studies by Laine and Palovaara are conflicting.

- Laine shows an increase in AUC and Cmax following a an unspecified time period on regimens for (three subjects gestodene 75 ug/ethinylestradiol 30 ug) and (one subject a triphasic preparation containing levonorgestrel 50-125 ug/ethinylestradiol 30-40 ug).

- Palovaara showed no mean effect on selegiline AUC and Cmax following a 10 day regimen of 2 mg estradiol valerate and 250 ug levonorgestrel.

- The only similarity in the two studies is the levonorgestrel which is higher in the study by Palovaara. However in the Laine study levonorgestrel was studied in only one subject.

- The other problem is the large range and wide confidence intervals for the Laine study. The Palovaara data was less variable.

- These findings makes interpretation of the data very difficult and warrants further investigation by the firm to resolve the conflicting findings.

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COMPANION REVIEW NDA 19-334

This review was consulted to OCPB with these additional references added by the reviewer without an in-depth review of the article contents.

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OCPB Response:

There are two recent paper which discuss the effect of ethinylestradiol on CYP2C19 and hormone replacement therapy on CYP2B6 activity.

1. Clin Pharmacol Ther. 2003 Oct;74(4):326-33. Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation.

2. Br J Clin Pharmacol. 2003 Aug;56(2):232-7. The effect of ethinyloestradiol and levonorgestrel on the CYP2C19-mediated metabolism of omeprazole in healthy female subjects.

3.HEPATIC AND RENAL PATIENTS

Marked effect of liver and kidney function on the pharmacokinetics of selegiline.

Markku Anttila, MSc, Eero A. Sotaniemi, MD, t Olavi Pelkonen, MD, and Arja Rautio, MD Turku and Oulu, Finland
CLINICAL PHARMACOLOGY & THERAPEUTICS 2005;77(1):54-62

This study comprised of 40 volunteers (21 women and 19 men) who were classified into 4 groups(10 each) according to their liver and kidney function (Table 1).

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Table I. Demographic characteristics of subjects

Subjects	*Control*	*Impaired liver function*	*Drug-induced liver function*	*Impaired kidney function*
Sex				
Men	3[illegible]	7	2	7
Women	7[illegible]	3	8	3
Age (y)				
Mean ± SD	56.4 ± 6.8	57.9 ± 8.0	53.5 ± 8.2	68.4 ± 6.1
Range	48-68	47-69	45-71	57-76
Weight (kg)	63.5 ± 10.4	87.8 ± 16.8	68.9 ± 14.3	78.0 ± 13.6
Height (cm)	163.3 ± 9.4	174.2 ± 10.1	163.7 ± 9.4	168.3 ± 7.8
Body mass index (kg/m^2)	23.7 ± 3.0	28.7 ± 3.4	25.5 ± 3.8	27.6 ± 2.8
Serum chemistry studies*				
AST (U/L)	23.9 ± 9.3	46.4 ± 29.7	24.6 ± 7.4	27.6 ± 10.2
ALT (U/L)	23.1 ± 7.7	64.1 ± 53.3	30.5 ± 12.1	33.6 ± 25.7
Alkaline phosphatase (U/L)	127 ± 30	253 ± 164	176 ± 66	172 ± 70
γ-Glutamyltransferase (U/L)	25.2 ± 38	254 ± 422	57.4 ± 35.5	36.1 ± 11.1
PIIINP (μg/L)	3.48 ± 0.68	5.47 ± 2.30	3.06 ± 0.78	4.10 ± 0.89
Urea (mmol/L)	5.19 ± 1.20	5.67 ± 1.94	5.38 ± 1.56	12.2 ± 8.2
Creatinine (μmol/L)	78.0 ± 15.1	79.6 ± 11.9	79.6 ± 11.8	173 ± 121

Data are given as mean ± SD (n = 10 in each group).
PIIINP, Type III procollagen amino terminal peptide.
*The range of institutional normal values for the serum chemistry parameters are as follows: AST and ALT, 10 to 35 U/L; alkaline phosphatase, 50 to 200 U/L; γ-glutamyltransferase, 5 to 50 U/L; PIIINP, 1.7 to 4.2 μg/L; urea, 1.7 to 8.3 mmol/L; and creatinine, 55 to 115 μmol/L.

Subjects in group 1 (control group) included normal healthy subjects who had no evidence of liver or kidney disease. These subjects were ascertained to be in good health by medical history, clinical examination, and standard hematologic and blood chemistry tests before entering the study.

Patients in group 2 (liver disease group) had a diagnosis of liver dysfunction that had been confirmed histologically, and their liver function test results were abnormal and clearly distinguished from those of the control subjects. Although no Child-Pugh scores were provided the liver impaired patients serum chemistry was 2-10 fold higher than controls. There was no evidence of renal disease in these subjects since creatinine was comparable but urea was increased by only 10%.

Group 4 (kidney disease group) included patients with stable long-term renal impairment with elevated serum creatinine values.
Their liver function test results were in the normal range. Patients in group 4 were older on average than those in the other groups.

The subjects underwent a laboratory screening including liver and kidney function tests and glucose balance.

Subjects fasted from the evening (at least 12 hrs) before and until 3 hours after the drug administration. Smoking was not permitted during the fasting period. Intake of food containing large amounts of tyramine (aged cheese, yeast products) within 1 week before and 1week after the drug administration was not allowed.

Subjects were given a single dose of two 10-mg tablets of selegiline hydrochloride with 150 mL of tap water.

Venous blood samples (10 mL) were collected just before the drug administration and at the following times thereafter: 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 7, 10, 14, 24, 28, and 48 hours (17 samples).

Table III. Pharmacokinetic parameters of selegiline and its metabolites

Parameter	*Control*	*Impaired liver function*	*Drug-induced liver function*	*Impaired kidney function*	*One-way ANOVA*
Selegiline					
C_{max} (ng/mL)	3.14 ± 1.99	22.3 ± 32.0*	0.21 ± 0.16***	13.3 ± 14.5*	$F_{3,36} = 22.3$, $P < .001$
t_{max} (h)	0.5 (0.5-0.75)	0.63 (0.5-1)	0.5 (0.25-0.75)	0.5 (0.5-1)	Not applicable
AUC (ng · h/mL)	2.81 ± 2.30	50.4 ± 82.6*	0.12 ± 0.11***	16.7 ± 22.2*	$F_{3,36} = 21.7$, $P < .001$
Desmethylselegiline					
C_{max} (ng/mL)	48.8 ± 11.2	33.0 ± 20.7*	21.3 ± 9.7**	43.3 ± 14.2	$F_{3,36} = 5.0$, $P = .005$
t_{max} (h)	0.75 (0.5-1)	1 (0.5-1)	0.75 (0.5-1)	0.75 (0.5-1.5)	Not applicable
AUC (ng · h/mL)	101.5 ± 32.0	89.2 ± 62.3	31.3 ± 24.0***	141.0 ± 56.7	$F_{3,36} = 10.3$, $P < .001$
$t_{1/2}$ (h)	5.1 ± 2.3	10.6 ± 8.7	2.2 ± 2.8**	8.4 ± 3.1	$F_{3,36} = 11.3$, $P < .001$
l-Methamphetamine					
C_{max} (ng/mL)	27.6 ± 8.1	17.4 ± 7.9**	28.6 ± 8.2	23.4 ± 5.9	$F_{3,35} = 4.6$, $P = .009$
t_{max} (h)	2.25 (0.75-3)	3 (2-10)	2.5 (0.75-7)	2.25 (0.75-3)	Not applicable
AUC (ng · h/mL)	572 ± 141	464 ± 214	575 ± 29	957 ± 311**	$F_{3,35} = 7.4$, $P < .001$
$t_{1/2}$ (h)	14.0 ± 3.0	20.4 ± 6.0**	12.7 ± 3.4	28.2 ± 10.3***	$F_{3,35} = 17.6$, $P < .001$
l-Amphetamine					
C_{max} (ng/mL)	9.5 ± 2.8	5.0 ± 1.7***	14.6 ± 5.3*	6.0 ± 1.6*	$F_{3,33} = 15.2$, $P < .001$
t_{max} (h)	3.5 (1.5-10)	5 (1.5-14)	2.5 (0.75-5)	10 (1-24)	Not applicable
AUC (ng · h/mL)	287 ± 77	186 ± 56**	292 ± 103	413 ± 180	$F_{3,33} = 7.4$, $P < .001$
$t_{1/2}$ (h)	18.5 ± 3.9	28.2 ± 17.2*	12.5 ± 3.9**	41.9 ± 11.8***	$F_{3,33} = 22.0$, $P < .001$

Data are given as mean ± SD (n = 10), except for t_{max}, which is given as median and range.
C_{max}, Peak concentration; t_{max}, time to peak concentration; AUC, area under serum concentration–time curve; $t_{1/2}$, terminal half-life.
*$P < .05$ (pairwise comparison with normal subjects).
**$P < .01$ (pairwise comparison with normal subjects).
***$P < .001$ (pairwise comparison with normal subjects).

The mean pharmacokinetic parameters are listed in Table III. After the ingestion of two 10-mg selegiline tablets, the peak serum concentration of selegiline in control subjects was achieved in 0.5 hour, with an average peak serum concentration of 3.1 ng/mL (range, 0.4-5.8 ng/mL).

The peak serum concentrations and AUC values were, respectively, 7- and 18-fold higher (P < .05) on average in patients with impaired liver function and 15- and 23-fold lower (P < .001) on
average in patients with drug-induced liver function when compared with subjects with normal liver function.

In patients with impaired kidney function, peak serum concentrations and the AUC values of selegiline were approximately 4- and 6-fold higher (P<.05)respectively, than in control subjects.

Conclusions:

- In hepatic patients with impaired liver function liver serum chemistry was 2-10 fold higher than controls in this study.
- Hepatic patients showed peak serum concentrations and AUC values, respectively, 7- and 18-fold higher than controls.
- In renal patients with impaired renal function urea and creatinine levels were 2.5 fold higher than controls.
- Renal patients showed peak serum concentrations and the AUC values of selegiline approximately 4- and 6-fold higher than controls.

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REVISED OCPB LABELLING

FDA'S PROPOSED LABEL PHARMACOKINETICS

ZELAPAR™'s benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa in patients with significant OFF time.	b(4)
[redacted]	b(5)

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

✓ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 2

SIGNATURES

Andre Jackson_____

RD/FT Initialed by Raman Baweja,
Ph.D._____

Cc-NDA 21479, HFD-860(Jackson, Baweja,Rahman,Mehta),
Central Documents Room(Biopharm-CDR)

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/s/

Andre Jackson
9/21/2005 02:29:43 PM
BIOPHARMACEUTICS

Raman Baweja
9/21/2005 03:15:37 PM
BIOPHARMACEUTICS

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Clinical Pharmacology/Biopharmaceutics Review
Complete Response to AE letter

PRODUCT (Generic Name):	ZYDIS® Selegiline HCl
PRODUCT (Brand Name):	ZELAPAR ODT
DOSAGE FORM:	Orally Disintegrating Tablets (ODT)
DOSAGE STRENGTHS:	1.25 mg
NDA:	21-479
INDICATION:	Adjunct treatment for the management of **Parkinson's disease in patients who are** exhibiting deterioration of response to levodopa/carbidopa therapy
NDA TYPE:	Complete response to AE letter
SUBMISSION DATE:	3/31/05 5/27/05 8/3/05 8/4/05
SPONSOR:	Valeant Pharmaceuticals International.
REVIEWER:	Andre Jackson
TEAM LEADER:	Raman Baweja, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

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Comments to the MO Tyramine Study: 2

2.OCPB has requested the firm to conduct a food/fasting study as a Phase IV commitment to clarify the current information.

Summary of Requested Phase IV Commitments:

These items were included in the Approvable letter to the firm of February 7, 2003 but to date have not been addressed by the firm related to:

Drug Metabolism

1. The firm needs to better characterize the potential for selegiline or its metabolites to inhibit CYP450 enzymes by using in vitro drug concentrations above the IC_{50} for the enzyme.
2. The firm needs to look at the in vitro potential for the induction of CYP3A4, CYP1A2, 2A6, 2B6, and 2C8 metabolism by selegiline.
3. Additional drug-drug interaction studies may need to be considered depending on the information gathered on the metabolism of selegiline.

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

Food Effect

The firm has agreed to conduct another food study.

Liver and Renal studies

The firm has agreed to conduct these studies.

Age/Race

The firm should analyze their current single and multiple dose data to determine any effects of age/race on the pharmacokinetics of selegiline.

An Additional Phase IV Item has been requested based upon the review of Journal Articles related to the effect of Oral Contraceptives on Selegiline Pharmacokinetics (reference OCPB review of NDA-19334 submission dated July 21, 2003).

Oral Contraceptives

The firm should conduct a three-way cross-over between Premarin 0.625 mg daily and medroxyprogesterone acetate 5 mg, selegiline and ORTHO TRI-CYCLEN . The focus of the study would be to determine the effect of the contraceptive on selegiline pharmacokinetics.

Recommendations

1. The tyramine effect study results indicated no effect of seligiline on SBP in the presence of Tyramine greater than the positive control, however study design considerations must be addressed by the MO before the study can be found to be acceptable.
2. The thorough QT study showed that there was no increase in the QT interval over the positive control Moxifloxicin, so it can be concluded that selegiline has no impact on cardiac repolarization.
3. Meta analysis of single dose data and multiple dose data from the Tyramine study and the QT studies indicated no effect of gender on the pharmacokinetics of selegiline.

Andre Jackson
Clinical Pharmacology and
Biopharmaceutics
Division of Pharmaceutical Evaluation I

RD/FT Initialed by Raman Baweja, Ph.D._____

Cc-NDA21479, HFD-860(Jackson, Baweja, Rahman, Mehta), Central Documents Room(Biopharm-CDR)

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THE TYRAMINE EFFECT STUDY WAS REVIEWED BY VENEETA TANDON AND THE QT STUDY BY ANDRE JACKSON

STUDY RNA-ZEL-B-21-102: A phase I study in healthy subjects to evaluate the effect of steady state doses of ZELAPAR (Zydis selegiline HCl) on blood pressure responses to Tyramine

Study Objectives:

Primary: To evaluate the effect of ZELAPAR on potential blood pressure elevations induced by tyramine and to determine if ZELAPAR induces orthostatic hypotension.

Secondary: To assess whether the observed effects on tyramine induced blood pressure elevations were correlated to selegiline Cmax or other PK parameters and to evaluate safety and tolerability.

Study Design:

A multiple-dose, randomized, double-blind, double-dummy, placebo and positive controlled, parallel group study.

Population:

80 healthy older adult subjects (age ≥ 40 years), 16/treatment group to get at least 12 complete each treatment, 8 men and 8 women in each group

Treatments:

1.5 mg, 5 mg or 10 mg ZELAPAR, placebo and NARDIL 15/30 mg (phenelzine sulfate)

Primary PD variables:

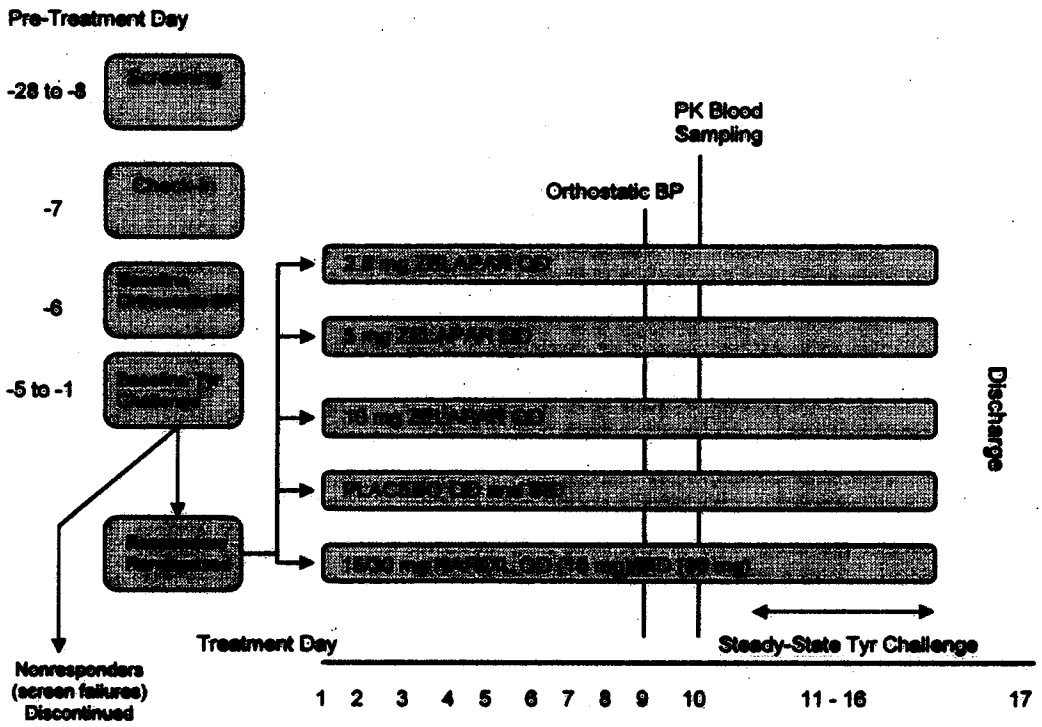
- Peak systolic blood pressure (SBP) response (Emax) following administration of highest dose of tyramine. Emax was determined as the highest change from the mean of three pre-dose SBP values
- The lowest dose of tyramine that produces a ≥ 30 mm Hg increase in SBP over the mean pre-dose value (threshold dose)

Primary Safety variables:

- The change from baseline in orthostatic blood pressure (SBP and DNP?) and steady state
- The proportion of subjects exhibiting orthostatic hypotension at steady state

The effect of ZELAPAR on tyramine-induced blood pressure elevations was determined by comparing the tyramine pressure response after 10 days of dosing to tyramine response at baseline prior to selegiline dosing.

The following is the schematic of the study design:



Tyramine Doses administered:

At Baseline: 25, 50, 100, 200 and 400 mg on consecutive days (Days -5 to -1)
At steady state: 12.5, 25, 50, 100, 200 and 400 mg on consecutive days (Days 11-16)

Subjects were required to fast for at least 8 hours prior to administration of tyramine and abstained from tyramine containing food for 5 days prior to the test and through the completion of the study. On tyramine dosing days lunch was served 3 hours after the tyramine dose.

Tyramine was given 10 minutes prior to the time scheduled for administration of the morning dose of study medication.

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Treatments administered:

Subjects that qualified for the study, based on having exhibited a minimum BP response to tyramine (3 consecutive SBP measurements ≥ 15 mm Hg higher than pre-dose values) were randomized to receive one of the 5 study treatments. The following treatments were administered.

Dose Group	Treatment	Study Days	Dosage	
1	ZELAPAR 2.5 mg	1-16	AM	Two 1.25 mg ZELAPAR tablets Six ZELAPAR placebo tablets One NARDIL placebo capsule
			PM	One NARDIL placebo capsule
2	ZELAPAR 5 mg	1-16	AM	Four 1.25 mg ZELAPAR tablets Four ZELAPAR placebo tablets One NARDIL placebo capsule
			PM	One NARDIL placebo capsule
3	ZELAPAR 10 mg	1-16	AM	Eight 1.25 mg ZELAPAR tablets One NARDIL placebo capsule
			PM	One NARDIL placebo capsule
4	Placebo	1-16	AM	Eight ZELAPAR placebo tablets One NARDIL placebo capsule
			PM	One NARDIL placebo capsule
5	NARDIL® 15 mg QD	1-3	AM	Eight ZELAPAR placebo tablets One 15 mg NARDIL capsule
			PM	One NARDIL placebo capsule
	NARDIL® 15 mg BID (30 mg)	4-16	AM	Eight ZELAPAR placebo tablets One 15 mg NARDIL capsule
			PM	One 15 mg NARDIL capsule

The morning dose of Zelapar (or Zelapar placebo) was administered without liquid and subjects did not ingest food for 5 minutes before or 5 minutes after taking the medication. The morning Nardil (or Nardil placebo) dose was taken with water approximately 5 minutes after administration of the Zelapar (or Zelapar) placebo tablet. Nardil or matching placebo was dosed BID, with the second dose 12 hours after the morning dose. Nardil tablets were overencapsulated for blinding purposes.

PK Sampling:

PK samples for the measurement of selegiline were taken on Day 10 at 0, 5, 10, 15 and 30 mins and 1, 2, 3, 4, 6, 8, 12 and 24 hours after the morning dose. Trough samples were also taken at day 8 and 9. Samples were analyzed using LC/MS/MS assay with a LOQ of 50 pg/ml. Assay validation was reviewed and found acceptable.

Selegiline in Plasma: Analytical Method

Method: HPLC/tandem mass spectrometry
Limit of Quantitation: 50 pg/mL in plasma.
Linearity: Range 50-5000 ng/mL
Accuracy: Inter-assay % CV less than 7.45%. Intra-assay % CV less than 8.77%.
Precision: Low control % CV less than 2.74%, medium control % CV less than 4.55%, high control % CV less than 0.98%.
Recovery: 80.44-83.10%
Freeze-thaw cycles: 3 cycles, % CV less than 3.70%
Benchtop Stability: Short term stability of analyte in matrix at room temperature: 24 hours; reinjection reproducibility:101 hours, 290 minutes at 4°C
Long term Stablity: Analyte in matrix at -20°C and -80°C: 8 days

Reviewer's Comment

1. The LLOQ of selegiline in the original NDA was 0.01 ng/ml and the methodology was Gas liquid chromatography with mass spectrometry analysis.

Pharmacodynamic measurements/methodology:

Baseline and Steady State Tyramine Challenge:

Baseline tyramine challenge test was begun on Day -5 and steady state tyramine challenge was begun on Day 11 at selegiline steady state.

Blood Pressure and heart rate measurements (Systolic and diastolic) :

On days tyramine was given, SBP, DBP and heart rate were measured 3 times at 10-minute intervals prior to dose administration. The mean of these 3 values was represented as the predose baseline value. Subjects will remain in semi-supine position. After administration of tyramine, heart rate and BP were measured at 10-minute intervals for the next 2 hours and for 15-minute intervals for the next hour (total 3 hours of monitoring).

Any subject exhibiting a significant hypertensive response to tyramine (SBP $\geq$ 180 mmHg and/or DBP $\geq$ 115 mmHg) during the baseline or steady-state tyramine challenge

was not advanced to the next higher dose of tyramine. Dose escalation could also be stopped for a given subject at the discretion of the investigator prior to reaching a hypertensive response based on the subject's symptoms and level of discomfort. Subjects exhibiting an increase of ≥ 15 mmHg in SBP over pre-dose measurements for three consecutive measurements (taken 10 minutes apart) at baseline were considered to be responders and were randomized to receive study medication. Any subjects that did not exhibit a minimum increase in systolic blood pressure of ≥ 15 mmHg in response to any dose of tyramine at baseline were considered non-responders and were removed from the study as screen failures prior to randomization.

Subjects that had a pressor response in SBP of 15-30 mm Hg were not precluded from advancing to the next dose of tyramine unless they also had achieved one of the defined maximum BP thresholds (SBP ≥ 180 mmHg and/or DBP ≥ 115 mmHg).

Subjects were considered to have completed the study once they reached a threshold response of ≥ 30 mmHg increase in SBP over pre-dose values during the steady state tyramine challenge or if they received all 6 doses of tyramine at steady-state without achieving the threshold SBP response.

The principle of the tyramime challenge test is to determine the threshold dose of tyramine necessary to produce a predefined pressure response (increase in SBP of ≥ 30 mmHg). The tyramine pressure response (TPR) is defined as:

TPR= Pre-treatment tyramine threshold dose/Post-treatment tyramine threshold dose

The higher the TPR, the greater the inhibitory effect of the drug. The comparison of TPRs between treatment groups involves the calculation of the ratio of the test TPR to the Control drug TPR or ratio of ratios. The log tyramine dose required to produce a threshold response was also determined.

Safety measurements:

In this review only orthostatic blood pressure measurements will be discussed, other safety will be evaluated by the Medical Officer along with the orthostatic blood pressure measurements.

Orthostatic Blood Pressure measurements:

Orthostatic BP measurements were taken on Day -6 and -5 and Day 9 and 10. On day -5 and 10 a 24 hour orthostatic BP measurement at 8 am. SBP, DBP and HR were recorded at rest after the subject had been supine for 5 minutes and then again after the subject had been standing for 2 minutes. The orthostatic BP and HR were recorded at predose, 0.5, 1, 2, 4, 6, 8, 10 and 24 hours after the morning dose of the study medication. BP measurements were performed at the same arm for each subject throughout the study.

Primary Pharmacodynamic Analysis:

The following PD variables were evaluated:

1) **Change from baseline in SBP at the highest tyramine dose on treatment:**

The first primary effect analysis was conducted to determine whether ZELAPAR potentiates the effect of tyramine on SBP. The analysis was conducted on the ITT population.

The peak systolic blood pressure response (Emax) was defined as the highest increase in SBP (change from pre-dose, where the pre-dose value is the average of the three pre-dose SBP measurements) following administration of the highest tyramine dose. For this analysis the response measure, change from baseline in peak SBP response, was the difference between the Emax for the largest dose of tyramine during steady-state and the Emax for the corresponding dose of tyramine during baseline.

For each subject, the change from baseline calculation was made within the same tyramine dosage level (fixed as the highest tyramine dose received during randomized treatment). For example, if the highest tyramine dose received during randomized treatment was 200 mg, the change from baseline calculation was the Emax value at 200 mg during randomized treatment minus the Emax value for the 200 mg dose during the baseline period.

2) **Log tyramine dose at threshold response:**

The second primary effect analysis was conducted to estimate the relative difference in the tyramine threshold dose. The tyramine threshold dose was defined as the lowest dose of tyramine observed to produce a $\geq$ 30 mmHg increase in SBP.

Following log-transformation (natural log) the log-tyramine threshold doses observed during randomized treatment were compared using the two, one-sided test procedure. The analysis was conducted on the ITT population. Each dose of ZELAPAR (T or test treatment) was compared with NARDIL or placebo (R or reference treatment). A ratio of the test to reference (T/R) log-tyramine threshold doses significantly > 1.00 indicated that the dose of tyramine required to produce the threshold response was significantly higher following treatment with ZELAPAR than following treatment with NARDIL. The inverse of the point estimate for the T/R ratio was an estimate of the relative potency of ZELAPAR to NARDIL.

Primary Safety Analysis:

Effect of ZELAPAR on Orthostatic Blood Pressure:

A series of orthostatic blood pressure and heart rate measurements were obtained for each subject over a 24-hour period at pre-treatment baseline (Day -6) and toward the end of

dosing to steady state (Day 9). The difference between the Day 9 values and the Day -6 values was the response variable for this analysis. Each active treatment group was compared to placebo at each time point.

The proportion of subjects exhibiting clinically significant orthostatic hypotension (decrease in SBP ≥20 mmHg or DBP ≥10 mmHg) was calculated. This analysis was conducted on the Safety population. Each of the active treatment groups was compared to placebo with respect to orthostatic hypotension using Fisher's exact test. Sample time deviations and dose administration data were presented in listings.

Secondary Pharmacodynamic Analyses:

Secondary pharmacodynamic analyses included the following:

1) **Threshold Dose Ratios**:

This analysis examined the effect data using the "classical approach". A threshold tyramine dose (lowest dose which produces a "sustained" ≥30 mmHg increase in SBP) was calculated for each subject at baseline and on randomized treatment. For the purpose of this analysis a "sustained" response was defined as an increase in SBP ≥ 15 mmHg at two consecutive time points (taken 10 minutes apart) where one of the increases was ≥ 30 mmHg. The ratio of the baseline threshold dose to the on-treatment threshold dose was computed for each subject. These ratios were compared between the active treatment groups and also to placebo. Only those subjects that meet the response criteria at baseline and on-treatment were included in the analysis.

2) **Effect of Tyramine Threshold Dose Definition:**

The second primary effect analysis (log tyramine dose at threshold response) was repeated using two alternative defnitions of the tyramine threshold dose: a) the lowest tyramine dose producing an increase in SBP ≥ 15 mmHg at two consecutive time points taken 10 minutes apart where one of the increases was ≥30 mmHg; or b) the lowest tyramine dose producing an increase in SBP ≥ 30 mmHg at two consecutive time points taken 10 minutes apart. The analysis, model and presentation of results were the same as that outlined for the second primary effect analysis.

3) **Correlation of blood pressure response to tyramine challenge with the peak blood concentrations of selegiline:**

On Study Day 10, eleven blood samples were taken from each subject for the analysis of selegiline concentration. The peak effect on SBP (Emax) at the highest tyramine dose was correlated with selegiline Cmax. A linear correlation coefficient was calculated.

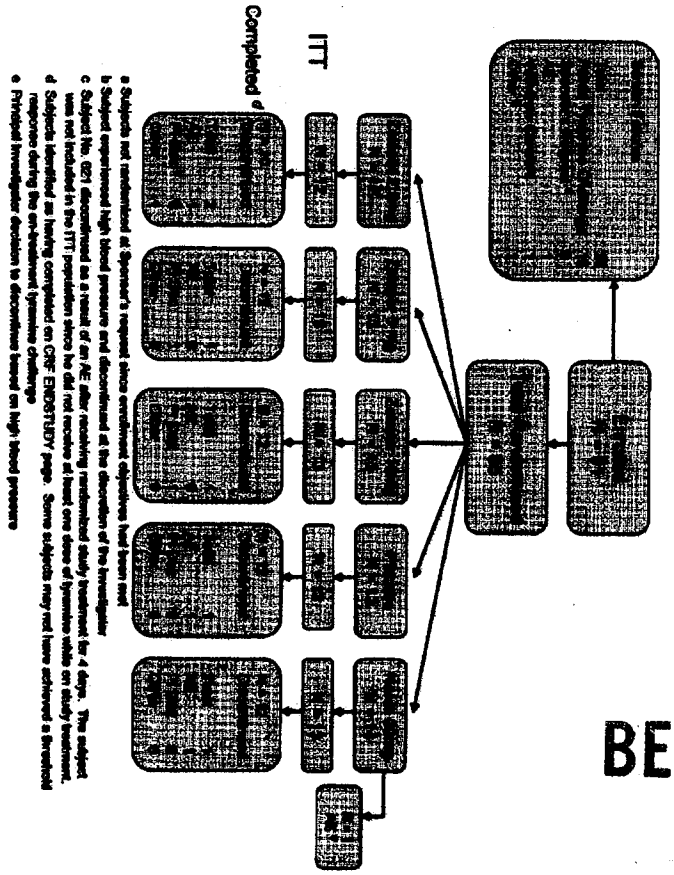
4) **Change from baseline in peak SBP at each tyramine dose on treatment:**

The change from baseline in peak SBP response (Emax) was calculated for each subject at each tyramine dose level. Each of the active treatments was compared to placebo at each tyramine dose level using the analysis methods described for the first primary effect analysis (change from baseline SBP at the highest tyramine dose on treatment). An analysis was conducted on observed cases (including only those subjects with data at a given dose level); and a second analysis was conducted using the last-observation-carried-forward (LOCF) method to impute results for any tyramine doses not received while on treatment.

5) Change from baseline in peak DBP and pulse rate:

Change from baseline in peak DBP, mean DBP, and pulse rate was calculated for each subject at the highest tyramine dose on treatment. All active treatments were compared to placebo separately for each of these measures.

Subject Disposition:



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Pharmacokinetic Results:

Mean PK parameters for the ZELAPAR group are given below:

Parameter	ZELAPAR 2.5 mg N = 12	ZELAPAR 5 mg N = 13	ZELAPAR 10 mg N = 13
C_{max} (pg/mL)	1813.4 (858.1)	3554.3 (1350.6)	7921.3 (3356.7)
T_{max} (hr)[a]	0.50 (0.17 – 1.00)	0.50 (0.17 – 1.00)	0.50 (0.17 – 1.00)
AUC_{ss} (pg • hr/mL)	5040.0 (3287.1)	12518.6 (5523.2)	26125.4 (12949.4)
t ½ (hr)	7.1 (5.1)	11.7 (3.3)	10.9 (2.3)

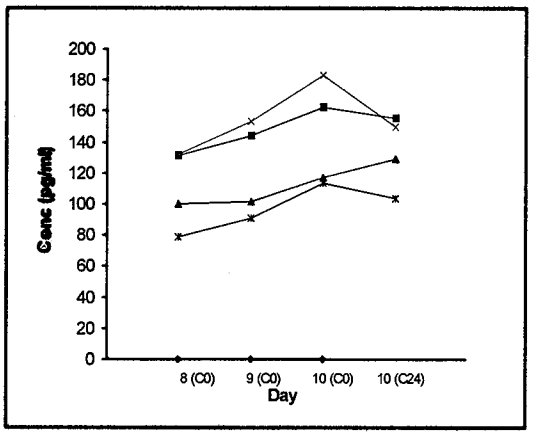
a Median (range)

Data Source: Supplemental Table 21

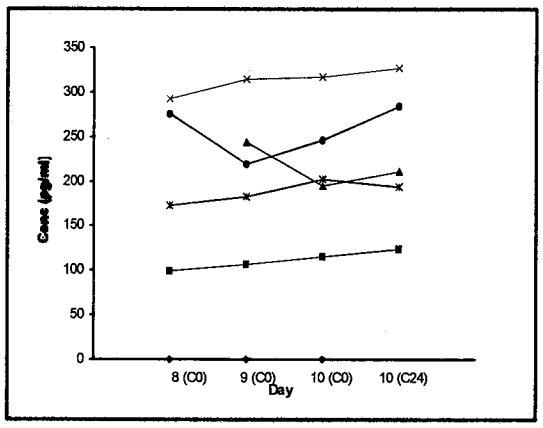
Reviewer's Comment:

1. The concentrations obtained from these study are within the variability range expected based on previous tyramine challenge study 101 from the original NDA.

2. The sponsor has not provided the assessment of steady-state at all the doses of ZELAPAR. From the dataset (both electronic and hard copy) it appears that the trough samples at Day 8 and 9 were not taken from all subjects:
There were a total of 4 subjects in the 2.5 mg ZELAPAR dose group, 5 subjects in the 5 mg ZELAPAR dose groups and 5 subjects in the ZELAPAR 10 mg dose group that had trough concentrations taken on Days 8 and 9. A total of 3 out 4 subjects in the 2.5 mg ZELAPAR dose group has concentrations below the LLOQ and 1 out of 5 in the ZELAPAR 5 mg dose group had concentrations below the LLOQ. The trough concentration data from the remaining subjects is shown in the following figures.



ZELAPAR 5 mg (N=4)



ZELAPAR 10 mg (N=5)