CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-336/21-708

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

New Drug Application – Major Amendment
Response to Approvable Letter
Clinical Pharmacology and Biopharmaceutics Review

NDAs:	21-336	21,708
Serial Numbers:	048 058	003 006
Generic Name:	Selegiline Transdermal	
Type of Submissions:	NDA (AZ) Major Amendement – Multiple Disciplines	
Formulation: **Strengths:** **Route:**	Transdermal Delivery System 20 mg / 20 cm^2 30 mg / 30 cm^2 40 mg / 40 cm^2 Topical	
Brand Names	EMSAM	
Sponsor:	Somerset Pharmaceuticals, Inc. Tampa, FL 33607	
Submission Dates:	May 26, 2005 August 31, 2005	
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.	

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II. EXECUTIVE SUMMARY

A. Contents of Submissions

Submission 048 contains the sponsor's formal response to the resubmission approvable letter for NDAs 21-336 and 21-708 dated January 30, 2004. This letter may be found in DFS folder [N 021-336 N 000 AZ 31-Jul-2003] in the following file:

M:\My Documents\NewDocs\WPDOC\NDS\21336&21708\second review cycle\actpack\AE letter with PI and PPI.pdf.

Submission 058 contains the sponsor's position regarding drug interactions with oral contraceptives and hormones for replacement therapy.

B. Background

The approvable letter contained the following items of interest to OCPB.

1) Labeling

2) Proposed regulatory dissolution specifications

3) Request for commitment to address the following issues as Phase IV commitments along with a request to submit a timeframe for completion.

   a. Dermal Adhesion Study

   b. Dermal Tolerability Study

   c. Performance of Selegiline Transdermal Systems in the Elderly

A copy of the OCPB requests for Phase IV Commitments included in the approvable letter of January 30, 2004 may be found in Appendix 2.

On December 21, 2004 the sponsor submitted a meeting request, (21-336 SN 045 and 21-708 SN 001), to discuss the approvable letter. The meeting package was submitted on January 13, and January 20, 2005 and a teleconference was held with the sponsor on February 9, 2005. Among the topics discussed were the OCPB Phase IV commitment requests.

Regarding the dermal adhesion and tolerability information, OCPB agreed that the information could be generated within a single study but as no information on tolerability scales had been provided comments on the appropriateness of tolerability scoring could not be provided.

With regards to the pharmacokinetic, pharmacodynamic and biopharmaceutic properties of selegiline transdermal systems in the elderly the sponsor asked whether a population PK analysis of available data, including new data from an open label safety study would address this issue. OCPB responded that this sort of data was unlikely to be sufficient, but that the data would need to be reviewed prior to formally concluding whether it would be likely to provide the requested information, and that a 6 month review clock would be necessary for any such review of a new population PK analysis.

OCPB notes from this teleconference and DNPDP meeting minutes may be found in DFS folder: [N 021336 N 000 MR 21-Dec-2004].

The OC/HRT DDI interaction submission is in response to a T-con between Dr. Laughren and the sponsor in August 2005.

IV. SIGNATURES

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

Ray Baweja, Ph.D. — Date

Team Leader
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-336
NDA 21-708
HFD-120 (BatesD, KleinD, OliverT, FreedL, DubitskyG, LaughrenT)
HFD-860 (KavanaghR, BawejaR, RahmanA, MehtaM)
Central Document Room (Barbara Murphy)

V. REVIEW

A. Labeling

See Appendix 1 for labeling comments.

B. Dissolution Specifications

Sponsor's Reply:

"Somerset has adopted the proposed dissolution method and specifications as the regulatory method. A copy of the revised specifications can be found in Section III, Tab #1."

Reviewer's Comment:

Section III, Tab #1 was not included in the desk copy provided to OCPB, the rest of the sponsor's response regarding dissolution is acceptable to OCPB.

C. Requests for Phase IV Commitments

For ease of review a copy of the OCPB requests for Phase IV Commitments included in the approvable letter of January 30, 2004 may be found in Appendix 2.

1. Dermal Adhesion and Tolerability Study

Sponsor's Reply:

"As per Somerset's February 9, 2005 teleconference and agreement with the Agency, Somerset will address Issue 1 and 2 (Adhesion and Tolerability) in one study as a Phase 4 commitment. Somerset will submit the proposed study protocol to the Agency for comments and/or agreement prior to initiation of the study."

Reviewer's Comment:

There is no proposed time frame. OCPB originally proposed — for completion and again recommends this time frame be committed to.

2. Phase IV Commitment – Elderly

Sponsor's Reply:

"Based upon the currently submitted data (see Tab I), Somerset feels that there are no age-related changes in the pharmacokinetics of selegiline or the pharmacodynamics of dietary tyramine during selegiline treatment that would compromise safety or require selegiline dose adjustments as one ages. In addition, the results of an open-label safety study of EMSAM 20 mg, 30mg, & 40mg in elderly depressed patients (S9309-P0204) will provide the necessary safety information requested for elderly subjects treated with EMSAM (see attached). Accordingly, with the additional information submitted in this response letter, Somerset feels that the requirements of ISSUE 3 have been met and will not require additional data in this subject population."

Reviewer's Comment:

The sponsor repeated the analysis that OCPB performed in the resubmission review and also found a statistically significant increase in selegiline exposure in women with age. (N.B. OCPB noted previously that this might be a chance finding.) Now that sampling times are known, the assumption used in the original OCPB analysis that all samples were drawn at 24 hours post-dose, is clearly in error, and this assumption may have resulted in the finding of a correlation of age with exposure.

The sponsor also provided a reference on selegiline dermal absorption (Pharm Res 1997:14(1) 50-55) and a review article on the effect of aging and transdermal absorption (Drugs & Aging 1192: 2(5) 432-449). The sponsor claims that these articles indicate there is no expected clinically relevant effect of aging on transdermal absorption that would necessitate a dosage adjustment. This conclusion is not justified. Instead the articles indicate that selegiline has sufficient polarity that decreased skin hydration with aging may decrease absorption. In addition, the effect of other dermal changes with aging, such as thinning skin is still not known.

The sponsor also has provided a population PK analysis of the effect of dose, age, and gender on Cl/F. This analysis claimed to have examined 1 Phase I study in males 55 – 78 yo and 6 phase II/III studies utilizing the to-be-marketed formulation. However the phase I study only examined the 20 mg to-be-marketed dose in 6 subjects and we don't know the age of these subjects and no PK data from this study was provided. In addition, as only 2 of the phase II/III studies included subjects greater than 65 yo, the review focused on these two studies. (See Table 6 in Appendix 4 for a summary of the studies in the sponsor's pop PK analysis.)

The two studies enrolling elderly subjects included doses of 20, 30, and 40 mg. Where as the other 4 studies only included doses up to 20 mg. A breakdown of the number of samples in the sponsor's population PK analysis from the studies with elderly subjects is shown in Table 1. More importantly Table 2 shows the small number of subjects of the extreme elderly which is of most interest.

Table 1 Breakdown of number of samples in Sponsor's Population PK Analysis from Studies with Elderly Subjects (Studies 052 and 204)[a]

Study	# Samples									
	Total	20 mg			30 mg			40 mg		
		Male	Female	Subtotal	Male	Female	Subtotal	Male	Female	Subtotal
Study 052	207	12	12	24	51	82	133	17	33	50
Study 204	48	7	9	16	7	9	16	7	9	16
Both Studies	255	19	21	40	58	91	149	24	42	66

a N.B. Excludes outliers

Table 2[a] Breakdown of Number of Subjects and Samples Available from Studies with Elderly Subjects by Age Group (Studies 052 and 204)[a]

Age Range (years)	Group	# Subjects	# Samples
18-64	Young Adults	117	201
65-75	Young Elderly	12	39
>75	Old Elderly	7	17
≥18	Total	136	257

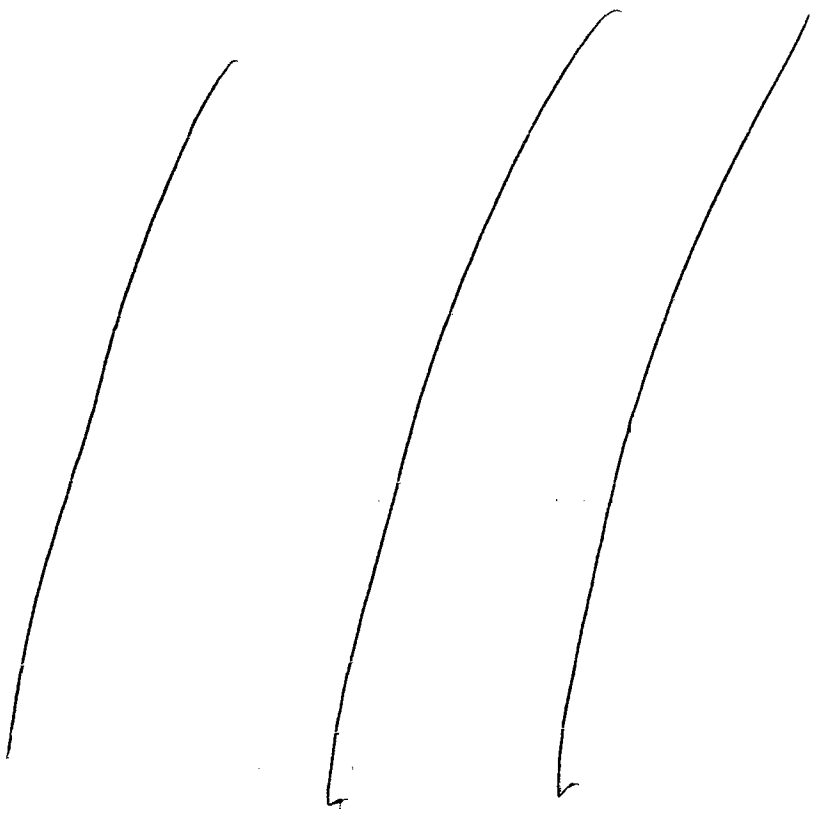
a – N.B. Includes outliers

The difference in the number of samples between Table 1 and Table 2 is due to the sponsor excluding outliers, i.e. samples $\geq$ 3 standard deviations above the mean.

As expected with such a small number of samples the sponsor did not find any effect of age.
Other deficiencies in the sponsor's analysis include the lack of any information on the metabolites as requested and questions about the sampling times, as although the samples were supposed to be 24 hours samples they range from 0 - > 600 hours post dose. Even censoring samples drawn > 48 hours post dose it's still unclear whether a dose was given around 24 hours or not.

Figure 1 shows all the data from the phase II/III studies up to 48 hours post-dose by dose, age range, and gender. By inspection exposures appear to be dose proportional, independent of gender, and with no clear effect of age. What are most striking are the outliers. Although the sponsor excluded these 5 data points based on statistical criteria, further examination reveals that the 2 outliers at 20 mg are in the same subject several weeks apart, and that all outliers at doses of 30 mg and 40 mg were in 2 elderly subjects, (1 male and 1 female). Thus the replication of high exposures in 2 of these 3 subjects clearly indicates that these high exposures are not by chance alone and that they are presently unpredictable. In addition, the higher incidence of high exposures in the elderly does not serve to ameliorate our concerns with higher exposures in the extreme elderly.

Figure 1 Selegiline Concentration vs. Time After Dose (TAD) up to 48 Hours by Gender, Dose and Age Group for all Data for all Studies



Appendix 5 shows the progression of the exploratory data analysis performed. When corrected time after dose is used it was assumed that a dose was administered at 24 hours.

The remainder of the sponsor's response to this phase IV request with respect to tyramine effect is being reviewed by the medical officer. However the sponsor does not address other concerns regarding pharmacodynamic changes responses with age, e.g. CNS and cardiovascular effects. (See Appendix 2 for the Phase IV request).

It's interesting to note the distribution of doses from phase III study 052, the data seems to indicate that > 90% of subjects require a dose of greater than 20 mg. (see Table 3)

Table 3 Distribution of Dosing in Subjects for Whom PK Sampling was Performed, (study 052)

Doses at which PK Samples Drawn (mg)	Subjects for these dosage PK Samplings (N)	Highest Dose Level Achieved (mg)	Total Subjects Achieving Highest Dose Level	% of Subjects Achieving this Dose Level
20 only	5	20	10	8.6
20 & 20	5			
30 only	26	30	60	51.7
20 & 30	5			
30 & 30	29			
40 only	1	40	46	39.7
30 & 40	45			
20 & 40	—			
20 & 30 & 40	—			
All Doses	116	—	116	100.0

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D. Drug – Drug Interactions with Oral Contraceptives and Hormone Replacement Therapy

In submission NDA 21-336 / 21,708 SN 058/ 006 submitted August 31, 2005 the sponsor addressed the issue of potential interactions with oral contraceptives and HRT raised by Dr. Laughren on August 24, 2005.

The gist of the sponsor's arguments follows:

- EMSAM is administered transdermally, avoids first pass by the liver, and thus a decrease in hepatic first pass would be less likely to result in a multifold increase in bioavailability.
- EMSAM is metabolized by multiple pathways, and specific inhibitors of individual pathways, (i.e. 3A4 and 2A1) failed to result in significant pharmacokinetic interactions.
- Literature references from the same group result in conflicting information.

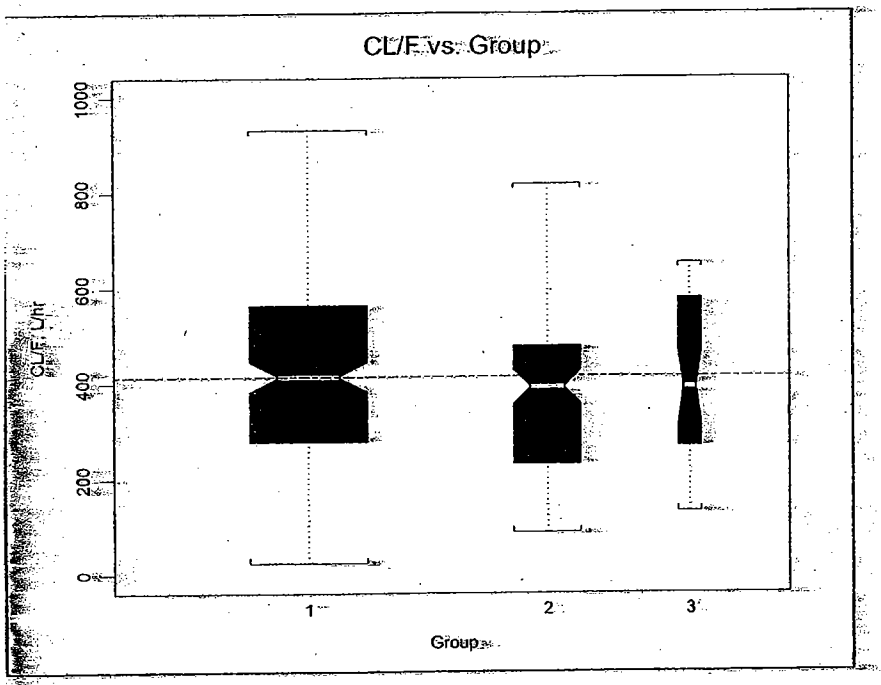
  Laine et al: Br J Clin Pharmacol 47:249-254, 1999

  Palovaara et al. Eur J Clin Pharmacol 58: 259-263, 2002

  (These studies have been previously reviewed by Dr. Andre Jackson of OCPB for an internal consult to DPP, (See NDA 19-338 Selegiline Oral Tablets submission date July 21, 2003)).
- There is no evidence of an interaction from phase III population PK data, (see Figure 2).

Figure 2 Selegiline Post-Hoc Cl/F Estimates in Females with and without Oral Contraceptives and Hormone Replacement Therapy from Study A9303-P0401.2

Figure 1: Selegiline CL/F with Respect to Co-medications in MDD Patients



Patient Group = (1) no co-medication, (2) Hormone replacement therapy, (3) Oral contraceptives. The median of each subgroup is shown as the white band inside the color box and the horizontal dashed line represents the median for group 1 patients. The limits of each box represents the 25 to 75 percentile. The extreme bars represent the 95% C.I.

Review Comments:

Even when there is a known drug-drug interaction population PK analyses may not detect an interaction due to a variety of reasons. In the present case insufficient data was provided to evaluate the data provided.

Any interaction depends not only on the route of administration, but also the dose, regimens, and specific drugs involved. With regard to the population analysis performed the sponsor utilized data from study A9303-P0401.2. Sampling information provided is shown in Table 4, however, no additional information on the study was provided. Appendix 4 shows the phase II/III studies from the pop PK analysis for the elderly question. Study A9303-P0401.2 examining the effect of OCs and HRT is not among the studies used in the population PK analysis of age and gender. Thus we don't know even basic information such as subject age, when the samples were drawn, or even if subjects were even on selegiline and the OC or HRT at the same time.

Table 4 Pop PK Sampling in Women for Study A9303-P0401.2.

Group	Number of Females	Number of Samples
Selegiline Alone	106	223
Selegiline + OCs	57	128
Selegiline + HRT	21	44
Total	184	395

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_____ Deliberative Process

Appendix 2 OCPB Phase IV Commitment Requests from January 30, 2004 Approvable Letter

3. We request that the sponsor examine the following issues as phase IV commitments and commit to submitting study reports for them; please propose time frames for the submission of the reports following approval of the NDAs. Reports should be submitted to NDA 21-336, with letters of cross-reference submitted to NDA 21-708, assuming both NDAs are approved concurrently.

ISSUE 1 Adhesion

Please provide information regarding the adhesion properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), over a 3 week period under conditions approximating actual use.

The following factors are to be examined in this study:

- Subject age
  - i.e. young healthy adults, the elderly (i.e. 65 – 84 yo), and the extreme elderly (i.e. $\geq$ 85).
- Application to the different labeled application sites including the upper torso and upper arm.

For each study arm 100 completers are anticipated.

The data generated should also be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

ISSUE 2 Dermal Tolerability

Please provide information regarding the dermal tolerability of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), over a 3 week period under conditions approximating actual use.

The following factors are to be examined in this study:

- Subject age
  - i.e. young healthy adults, the elderly (i.e. 65 – 84 yo), and the extreme elderly (i.e. $\geq$ 85).
- Application to the different labeled application sites including the upper torso and upper arm.

For each study arm 100 completers are anticipated.

The data generated should also be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

ISSUE 3 Performance of Selegiline Transdermal Systems in the Elderly

Only 3 subjects studied were $\geq$ 65 years of age. All three were women and the eldest was 70 years old.

Consequently, please provide information regarding the pharmacokinetic, pharmacodynamic and biopharmaceutic properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2); in young healthy adults, the elderly (i.e. 65 – 84 yo), and the extreme elderly (i.e. $\geq$ 85). The effects of gender and ethnicity/race should also be examined for each age range.

Information provided for each age group, should include complete pharmacokinetic profiles of selegiline and the 3 metabolites previously examined, the tyramine response, MAO selectivity, drug delivery, and safety information by age.

With regards to safety we are specifically interested in CNS effects, as well as differences in blood pressure changes; especially as the elderly typically have higher baseline systolic blood pressure and are at risk for orthostatic hypotension.

Appendix 3 Proposed Dissolution Method January 30, 2004 Approvable Letter

Please adopt the following dissolution method and specifications as the regulatory method.

Table 5 Dissolution Method and Specifications

Formulation(s)	**20 mg / 20 cm^2 and 30 mg / 30 cm^2**	**40 mg / 40 cm^2**
Media	0.1 M Potassium Phosphate Buffer Monobasic pH 5	0.1 M Potassium Phosphate Buffer Monobasic pH 5
Volume	500 ml	***1000 ml***
Temp (°C)	32 ± 0.5	32 ± 0.5
Apparatus	USP 5 Paddle over disk	***USP 6 Rotating Cylinder***
RPM	50	50
Sampling Times and Specifications (% LC)	1 hr — 4 hr — 8 hr — 24 hr NLT	1 hr — 4 hr — 8 hr — 24 hr NLT —
Acceptance Criteria	Per acceptance table 4 in TRANSDERMAL DELIVERY SYSTEMS—GENERAL DRUG RELEASE STANDARDS USP 26-NF 21 2nd Suppl., section<724> DRUG RELEASE	

Appendix 4 Phase II/III Studies included in Population PK Analysis

Table 6 Phase II/III Studies included in Population PK Analysis

Study #	Study Design	Age Range (yrs)	Disease	Patch Strengths (mg)	Sampling Time	Sampling Day
P0052	**Flexible Dose, DB, PBO-Ctrl, Parallel**		**MDD**	**20, 30, 40**	**Prior to removal**	**Baseline, Week 3, Week 8**
E106-96B	Rand, DB, PBO-Ctrl	18-65		20	Prior to removal	Baseline, Week 3, Week 8
E113	Rand, DB, PBO-Ctrl	18-65		20	Prior to removal	Baseline, Week 4, Week 8
E114	Rand, DB, PBO-Ctrl	18-65		10/20, 20	Prior to removal	Baseline, Weeks 1, 3, 5
P0204	**52 week OL Safety**	**≥18**	**MDD**	**20, 30, 40**	**Prior to removal**	**Baseline, Week 4, Week 9**
P9804	Rand DB, PBO-Ctrl	18-65		20	Prior to removal	Baseline, Week 4, Week 8

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/s/

Ron Kavanagh
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Raman Baweja
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New Drug Application – Response to Approvable Letter
Clinical Pharmacology and Biopharmaceutics Review

NDAs:	21-336 21-708
Type of Submission:	NDA (AZ) Major Amendment – Multiple Disciplines Meeting Request for T-Con SN: 045 / 001
Generic Name:	Selegiline Transdermal
Formulation:	Transdermal Delivery System
Strengths:	20 mg / 20 cm^2 30 mg / 30 cm^2 40 mg / 40 cm^2
Route:	Topical
Brand Names	EMSAM
Sponsor:	Somerset Pharmaceuticals, Inc. Tampa, FL 33607
Submission Dates:	December 21, 2004
Date of T-Con:	February 9, 2005
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

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2 INTRODUCTION / BACKGROUND

2.1 Clinical Pharmacology

Selegiline is a selective, irreversible inhibitor of MAO-B used for the treatment of depression and Parkinson's Disease. Although selegiline is selective for MAO-B at low doses, at oral doses in the range of 10 mg – 25 mg daily, selectivity is lost. Drug delivery information suggests that doses of 11 – 12 mg may be achieved with transdermal selegiline and there is the potential that this could be higher in the elderly.

According to the sponsor, 'Transdermal selegiline administration results in sufficiently high CNS concentrations that CNS MAO inhibition is nonselective. Nonselective CNS MAO inhibition is thought to be necessary for the antidepressant effect of selegiline. However, transdermal administration is thought to limit inhibition of intestinal MAO-A which detoxifies dietary amines (e.g., tyramine) and drugs such as dopamine, and thereby limits the risk of hypertensive crisis due to 'cheese reactions'. In addition, transdermal selegiline avoids first-pass selegiline metabolism reducing metabolism to amphetamine.'

2.2 Regulatory History

2.2.1 Oral Selegiline

Selegiline is currently approved in the US for oral administration for Parkinson's disease in patients on carbidopa / levodopa who continue to deteriorate.

The recommended regimen for the administration of ELDEPRYL is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

2.2.2 EMSAM™ - Selegiline Transdermal System

2.2.2.1 Original NDA

EMSAM (selegiline transdermal system, (STS)) 20 mg / 20 cm^2 was originally submitted for treatment of depression under NDA 21-336 on May 24th, 2001, (letter date: May 21st, 2001). A not-approvable letter was issued May 25th, 2002, due to the lack of a 2nd positive efficacy study.

In addition to the non-approval for lack of evidence of efficacy, the not-approvable letter made the following points that are of interest to OCPB:

- Cheese Reaction

Although the data submitted generally support the removal of dietary restrictions with STS, the tyramine pressor dose in challenge studies tended to decrease over time (up to 33 days). Consequently the sponsor was asked to provide reassurance that there is not a continuing decline in the pressor dose over

time by repeating the tyramine challenge testing after 60 days of use. In addition, if the pressor dose showed a continuing decline at 60 days, it would be necessary to also look at later time points.

- Contraindication of co-administration with TCAs, other MAOIs, and SSRIs

- Dissolution Data

At the time of the not-approvable letter the sponsor had proposed conducting additional studies utilizing higher dosages. Consequently the sponsor was reminded that if they chose to modify either the dissolution method or specifications, (e.g. by addition of higher strengths), then complete information to justify the proposed changes should be submitted.

In addition, under submissions N021336 N000 MR 29-Jan-2003 and N021336 N000 BC 13-Mar-2003 the sponsor proposed a change in the drug substance manufacturing site. In response OCPB recommended that the sponsor generate multi-point dissolution profiles as per the accepted method in the original NDA 21-336 and provide F2 calculations for comparison of dissolution profiles of the drug product manufactured using drug substance before and after the site change.

The original OCPB review can be found in DFS folder N021336 000 21-May-2001 and is dated February 28, 2002. Additional OCPB comments dated April 12, 2003 may be found in DFS folders N021336 N000 MR 29-Jan-2003 and N021336 N000 BC 13-Mar-2003.

2.2.2.2 NDA Major Amendment

On July 31st, 2003 the sponsor submitted a Major Amendment to all disciplines that included the following areas:

- An efficacy study in MDD at the previously studied dose of 20 mg / 20 cm^2, and at two additional higher dose strengths of 30 mg / 30 cm^2 & 40 mg / 40 cm^2.
- Tyramine effects over time and at the higher dose strengths.

Contents of the July 31st, 2003 submission that were of particular interest to OCPB include:

- Pharmacokinetics of new higher dosage strengths of 30 mg / 30 cm^2 & 40 mg / 40 cm^2 and the effect of intrinsic factors.
- Pharmacodynamic effects including tyramine dose response, time invariance of pharmacologic response, MAOI selectivity, and food effects.
- Drug-Drug Interactions
- Bioequivalence of application sites
- Drug Delivery Rate
- Adhesiveness and dermal tolerability in children
- Dissolution method and specifications for the new formulations

The sponsor's proposed Dosage and Administration Labeling and OCPB's summary of findings from this NDA amendment has been included in Appendix 1 for convenience to the reader.

3 CURRENT SUBMISSION

The present submission requested a T-Con to discuss labeling and packaging artwork, and Phase IV commitments.

The following section contains a discussion of OCPB Phase IV commitment requests, the sponsor's replies and questions, and OCPB's comments.

3.1 OCPB Issues Requested to be Addressed as Phase IV Commitments in January 30, 2004 Approvable Letter

3.1.1 Phase IV Request - ISSUE 1: Adhesion

Please provide information regarding the adhesion properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), over a 3 week period under conditions approximating actual use. The following factors are to be examined in this study:

- Subject age
  - [i.e. young healthy adults, the elderly (65 – 84 years old), and the extreme elderly (≥ 85)].
- Application to the different labeled application sites including the upper torso and upper arm.

For each study arm 100 completers are anticipated.

The data generated should be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

3.1.2 Phase IV Request - ISSUE 2: Dermal Tolerability

Please provide information regarding the dermal tolerability of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm2 to 40 cm2), over a 3 week period under conditions approximating actual use. The following factors are to be examined in this study:

- Subject age
  - [i.e. young healthy adults, the elderly (65 – 84 years old), and the extreme elderly (≥ 85)].
- Application to the different labeled application sites including the upper torso and upper arm.

For each study arm 100 completers are anticipated.

The data generated should also be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

3.1.2.1 Sponsor's Reply and Questions to Issues 1 and 2

3.1.2.1.1 Issue 1: Adhesion / Issue 2: Tolerability

Since the basic design of the adhesion and tolerability studies is the same, Somerset proposes to conduct one study, which can address both issues. Secondly, we request that the subject population of the study comprise two age groups; less than 65 years and equal to or greater than 65 years. We have chosen these two age groups for the following two reasons: (a) there are no published studies to the best of our knowledge that show adhesion characteristics of a TDS to be different in subjects between 65 and 84 years and ≥85 years; and (b) the difficulty and feasibility of recruiting subjects greater than 85 years of age. This information was obtained in conversations with individuals from two reputable contract research organizations.

If we are able to reduce the study population to two groups, no restrictions on age will be placed on the elderly (~ 65 years) group. Therefore, if a sufficient number of subjects (≥85 years of age) enter the study, those subjects would be analyzed separately to fulfill the original request by the Agency.

A copy of the protocol synopsis for the proposed adhesion/dermal study is provided in Tab IIA of this document.

3.1.2.1.1.1 Sponsor's Question 1:

Somerset would like the Agency's concurrence that the proposed adhesion/tolerability study, as described in Tab IIA of this document, will satisfy the Phase IV-Issue #1 commitment as requested in the Agency's January 31, 2004 Approvable Letter.

3.1.2.1.1.2 OCPB Comments

The protocol synopsis of the combined dermal adhesion and dermal tolerability study may be found in **Appendix 2**.

OCPB agrees that both the dermal adhesion and dermal tolerability issues can be addressed in a single study. In fact OCPB anticipated that this would be most feasible approach.

OCPB also agrees that the subject population of the study comprise two age groups; less than 65 years and equal to or greater than 65 years.

OCPB requests that the sponsor try to enrich the study with elderly subjects, especially the old elderly.

Assuming that this would result in a ratio of 3:1 of young and middle aged subjects to elderly and a ratio of 4:1 for young elderly compared with old elderly, we still don't expect to see sufficient numbers of old elderly to give an accurate portrayal, (see Table 1).

Table 1 Estimates of Number of Subjects by Age in Adhesion and Tolerability Studies

TDS Strength	Number of Subjects					
	Enrolled	Completers	OCPB Estimates by Age			
			Young & Middle Aged Adults 18 – 64 yo	All Elderly ≥ 65 yo	Young Elderly 65 – 84 yo	Old Elderly ≥ 85 yo
20 mg / 20 cm^2	125	100	75	25	20	5
30 mg / 30 cm^2	125	100	75	25	20	5
40 mg / 40 cm^2	125	100	75	25	20	5

However, the majority of patients are not expected to be elderly and we typically have not asked for tolerability and adhesion data in the elderly when it's not the primary population of interest. Therefore, labeling indicating the limitations of the study and the possibility of worse tolerability with advancing age may be appropriate.

A complete protocol is still needed in order to evaluate the scoring systems used for adhesion and tolerability.

Descriptive statistics of adhesion as a percent of total of applications and as a percentage of time, and percentage of patients with various tolerability scores are advised, as we typically have used tables of such descriptive statistics in labeling.

3.1.3 Phase IV Request - ISSUE 3: Performance of Selegiline TDS in the Elderly

Only 3 subjects studied were ≥ 65 years of age. All three were women and the eldest was 70 years old.

Consequently, please provide information regarding the pharmacokinetic, pharmacodynamic and biopharmaceutic properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), in young healthy adults, the elderly (i.e. 65 – 84 y ears old), and the extreme elderly (i.e.≥ 85).

The effects of gender and ethnicity/race should be examined for each age range.

Information provided for each age group should include:

- complete pharmacokinetic profiles of selegiline and the 3 metabolites previously examined,
- the tyramine response
- MAO selectivity
- drug delivery
- safety information by age

With regard to safety we are specifically interested in CNS effects, as well as differences in blood pressure changes, especially as the elderly typically have higher baseline systolic blood pressure and are at risk for orthostatic hypotension.

3.1.3.1 Sponsor's Reply and Questions to Issue 3

For the purpose of addressing Issue #3, Somerset has divided this issue into three parts; pharmacokinetics (PK)/Biopharmaceutics, safety and pharmacodynamics (PD).

3.1.3.1.1 Part 1 - Pharmacokinetics/Biopharmaceutics

Somerset has conducted an extensive Phase I program in healthy volunteers to examine the pharmacokinetic/biopharmaceutic properties of the STS. This program included formal studies on patch delivery, relative bioavailability, duration of patch release, single-dose and multiple-dose pharmacokinetics for selegiline and each of its major metabolites, dose proportionality, drug-drug interactions, age and gender effects, and comparative studies in renal or hepatic impaired individuals. In these studies, the STS demonstrated predictable pharmacokinetic properties over a wide range of doses and subject populations without gender or age effects, or pharmacokinetic or clinically relevant drug-drug interactions (Appendix 1 and 2).

Somerset also obtained population pharmacokinetic data in the Phase III STS development program. These data included trough plasma levels of selegiline and each of its major metabolites in non-elderly (< 65 yrs, N=386) and elderly (> 65 yrs, N=28) patients with major depressive disorder, over the intended therapeutic dose range (dermally applied doses of 20mg/day - 40 mg/day). While some of these data were requested by the Agency, others were obtained to insure medication compliance, and to support the dose proportionality and the absence of an age effect (i.e. elderly vs. non-elderly), previously demonstrated in formal Phase I pharmacokinetic studies (Tab IIB).

In response to the Agency's concern for increased exposure to selegiline in the elderly (see FDA proposed Label; "Population Subgroups"- Tab IA), Somerset recently conducted a formal population pharmacokinetic analysis (Tab IIB) of the current STS Phase III pharmacokinetic database for major depression to explore the potential for an age effect on the apparent clearance of selegiline and each of its major metabolites. Body weight, creatinine clearance (estimated from serum creatinine, age and body weight), gender, and race (Caucasian and non-Caucasian) were also analyzed as variables that might affect the total body clearance of selegiline or its major metabolites. Up to 1082 plasma levels of selegiline and each of its major metabolites were obtained from 414 subjects (17 - 87 yrs) for the analysis. The effect of age was examined as a continuous variable (17 - 87 yrs) and as a categorical variable < 65 yrs vs. $\geq$ 65 yrs). Based upon this population pharmacokinetic analysis, no effect of age, gender or race was found on the apparent clearance of selegiline or each of its major metabolites. These results regarding age and gender are consistent with the formal pharmacokinetic studies previously conducted during the Phase I portion of the Somerset development program (see above) and further demonstrate that no increase in selegiline exposure occurs with age, gender or race.

3.1.3.1.1.1 Sponsor's Question 2:

Somerset would like the Agency's concurrence that the data provided herein satisfies the Phase IV- Issue 3(i) (PK/Biopharmaceutics) commitment as requested in the Agency's January 31, 2004 Approvable Letter.

3.1.3.1.1.2 OCPB Comments

The acceptability of this data is a review issue.

The sponsor has performed a population PK analysis by combining data from all studies previously submitted, along with additional data from a long term safety data. There are a number of potential issues with this approach including: the adequacy of sampling, use of different formulations and different bioanalysis in different studies, potential lack of information on application site and application, are there sufficient numbers of elderly with data (especially at the higher patch strengths), selection bias, are the baseline structural and variance models appropriate. In addition, the typical large variance seen in these

types of analyses may hide true differences. Thus no conclusions regarding whether this analysis satisfies the Phase IV request can be made until a complete review and possible reanalysis of the data is completed. This is likely to require a 6 month review clock as a major supplemental submission and a pharmacometric consult.

3.1.3.1.2 Part 2 - Safety in the Elderly

Somerset's ongoing, open-label safety study (S9303-P0204) has exposed over 100 patients, equal to or over the age of 65, to EMSAM 20mg, 30mg or 40mg. Within this study, Somerset is collecting safety data which we feel will satisfy the Agency's request.

A copy of the interim safety report, submitted with our NDA resubmission in July of 2003, is provided in Appendix 3 of this document. Within this report, safety data on CNS effects as well as blood pressure changes, as requested by the Agency, are presented in Section 5. Once completed, Somerset proposes to submit the final study report with safety results presented in the format provided herein.

3.1.3.1.2.1 Sponsor's Question 3:

Somerset would like the Agency's concurrence that the proposed data from the safety study, as described herein, satisfies the Phase IV-Issue 3(ii) (Safety) commitment as requested in the Agency's January 31, 2004 Approvable Letter.

3.1.3.1.2.2 OCPB Comments

This was addressed by the medical officer.

3.1.3.1.3 Part 3 - Pharmacodynamics

Although Somerset has conducted a large Phase I program on tyramine safety at administered STS doses of 15 mg to 40 mg in healthy volunteers, ranging in age from 18 to 63 years (mean 34.0 ± 13.1 years) (See summary of these data provided in Appendices 4 and 5), the Agency has requested that Somerset provide additional pharmacodynamic data relating to tyramine sensitivity in the elderly (≥: 65 years). Somerset feels that sufficient data has been provided to insure the safe administration of the 20 mg STS to elderly patients (as proposed in labeling- Tab IA) without the need for food restrictions and questions the need for additional tyramine studies for the following reasons:

1. No Change in Tyramine Sensitivity Factor with Age:

The ratio of the tyramine pressor doses at baseline and during treatment with the STS is referred to as the tyramine sensitivity factor (TSF). The TSF value corrects for variance among subjects in their sensitivity to the pressor effects of orally administered tyramine, and serves as a useful tool to examine the true pharmacological effect of the STS on the tyramine pressor response. Somerset has reviewed the Phase I tyramine challenge database of 18 to 58 year old subjects receiving the STS 20 mg continuously for 10 days and has compared the TSF values of each subject against their age (See Figures 1 and 2). No correlation was demonstrated between the subjects' age and their TSF value during STS treatment ($R^2 = 0.0012$). Similar results were obtained with dose-normalized TSF values obtained following 21 or 33 days of STS treatment with the 15mg to 40mg STS ($R^2 = 0.0015$). Thus, while we have not directly studied the tyramine response in subjects >65 years of age, these results indicate that there is no age-related change in the ability of the STS to increase the pressor response of orally consumed tyramine.

2. *No Change in Tyramine Pressor Dose with Age:*

It is also possible that the elderly are more responsive to the pressor effect of orally consumed tyramine, therefore requiring less tyramine than younger subjects to induce a hypertensive event during STS treatment. To investigate this possibility, tyramine pressor doses obtained during STS treatment were

compared to subject age (See Figures 3 and 4). No correlation was demonstrated between age and the tyramine pressor dose following 10 days of treatment with the 20 mg STS (R^2 = 0.0094). Similar results were obtained with dose-normalized tyramine pressor doses obtained following 21 or 33 days of STS treatment with the 15mg to 40mg STS (R^2 = 0.0488). These results indicate that elderly subjects will not be more responsive to tyramine.

3. *No Increase in Selegiline Exposure with Age:*

Another factor that could alter the tyramine pressor response is an age related increase in selegiline exposure. To investigate this possibility, Somerset recently conducted a formal population pharmacokinetic analysis of its current STS Phase III pharmacokinetic database for major depression. The effect of age was examined as a continuous variable (17 -87 yrs) and as a categorical variable < 65 yrs vs. ≥ 65 yrs). No effect of age was found on the apparent clearance of selegiline or each of its major metabolites (Tab 118). These data demonstrate that selegiline exposure is not increased with age.

4. *Elderly Out-Patients Administered the STS Without Dietary Restrictions Have Not Experienced Dietary-Induced Hypertensive Symptoms:*

Somerset continues to study the safety of the 20, 30, or 40mg STS in elderly (≥ 65 years) and non-elderly < 65 years) depressed patients (S9303-P0204), with a heightened awareness for adverse cardiovascular events. The majority of these patients are being administered higher doses (30 or 40 mg STS) of the STS and all patients are unrestricted regarding food or beverages. Currently, 104 elderly patients have completed 16 weeks, and 4 have completed 52 weeks of STS treatment.

Patients are queried for adverse events while taking the STS and vital signs are monitored at study visits. These data are specifically reviewed for hypertensive events that might be associated with dietary tyramine. To date no acute dietary-induced hypertensive events have been reported or observed.

The information presented above does not support the presence of an age related change in the tyramine pressor response during STS treatment. Thus it is unlikely that any new safety information will be gained from an additional study in the elderly. Elderly subjects are more likely to have undetected cardiovascular abnormalities that may pose a safety risk during the exposure to artificially high tyramine doses that are generally required to induce a hypertensive reaction in challenge protocols.

3.1.3.1.3.1 Sponsor's Question 4:

Somerset believes that the risk involved in exposing the elderly to tyramine pressor challenges is not warranted and requests that the Agency reconsider the request for additional pharmacodynamic studies in the elderly and remove the pharmacodynamic requirements from "ISSUE 3" of the approvable letter.

3.1.3.1.3.2 OCPB Comments

A summary of the sponsor's rationale is provided below along with OCPB comments.

Sponsor's Rationale	**OCPB Comments**
Somerset feels that sufficient data has been provided to insure the safe administration of the 20 mg STS to elderly patients (as proposed in labeling- Tab IA) without the need for food restrictions.	Information is only available on doses of 20 mg. Since dosages may range up to 40 mg information is incomplete. In addition, it may not be wise to have different recommendations for 20 mg and > 20 mg doses.
No change in tyramine sensitivity factor over the range of 18 to 58 years of age.	Extrapolation beyond the limits age limits studied is not appropriate.
No change in tyramine pressor dose over the range of 18 to 58 years of age.	Extrapolation beyond the limits age limits studied is not appropriate.
No increase in selegiline exposure with age as determined pop PK analysis.	The population PK analysis is a review issue, and there are expected deficiencies as mentioned previously. Prior analysis showed a possible upward trend in women. Finally, it's well known that skin thins with aging and that thinner skin allows greater drug absorption. Thus even though a categorical analysis of < 65 yo and $\geq$ 65 yo was performed, we might very well expect differences in absorption between a 95 yo and a 65 yo.
No tyramine related AEs have been noted in studies.	This sort of detection is expected to be insensitive to detecting an effect, due to the small number of elderly subjects, their relative health, the unknown likelihood of actually consuming a high tyramine containing meal, potential lack of recognition of AEs, potential lack of symptoms with BP changes, recall bias, and time differences between potential episodes and BP monitoring.
Elderly subjects are more likely to have undetected cardiovascular abnormalities that may pose a safety risk during the exposure to artificially high tyramine doses that are generally required to induce a hypertensive reaction in challenge protocols.	It is better to conduct a study under controlled conditions, where CV status can be screened for prior to study participation, and define the actual risk, rather than to risk severe reactions in the general population that may not be detected even with post-marketing surveillance.

4 OCPB DISCUSSIONS WITH THE SPONSOR DURING THE T-CON

Note:

On Friday, March 4, 2005 this section was reviewed and verbally approved by Dr. Mehul Mehta, OCPB DPE-1 Division Director, and was provided to the CSO to incorporate into the meeting minutes.

Issue 1: Adhesion / Issue 2: Tolerability

OCPB agreed that both the dermal adhesion and dermal tolerability issues can be addressed in a single study. OCPB anticipated that this would be most feasible approach.

OCPB also agreed that the subject population of the study may comprise two age groups; less than 65 years and equal to or greater than 65 years. However, OCPB requested that the sponsor try to enrich the study with elderly subjects, especially the old elderly.

With regards to the study design a complete protocol is still needed in order to evaluate the scoring systems used for adhesion and tolerability.

Descriptive statistics of adhesion as a percent of total of applications and as a percentage of time, and percentage of patients with various tolerability scores are advised as we have typically used tables of such descriptive statistics in labeling.

Labeling indicating [redacted] may be appropriate. However, this is a review issue.

ISSUE 3: Performance of Selegiline TDS in the Elderly

Part 1 - Pharmacokinetics/Biopharmaceutics

The acceptability of the population PK data is a review issue.

There are a number of potential issues with this approach including: the adequacy of sampling, possible lack of information on application site and application, and whether there are sufficient numbers of elderly subjects with data, (especially at the higher patch strengths). Thus no conclusions regarding whether this analysis satisfies the Phase IV request can be made until a complete review and possible reanalysis of the data is completed.

The sponsor asked if there was any particular information that we had seen in our review that raised concerns other than the trend previously mentioned with respect to PK in women in the phase III study data. Plus the sponsor questioned the premise that exposures might be different between young and old elderly. OCPB replied that there were no additional signals of concern noted during the review. However OCPB felt there was a paucity of information in the elderly. In addition, the well documented changes in skin thickness with aging and the relationship between skin thickness and transdermal absorption indicate that differences in absorption between the young elderly and the old elderly, e.g. a 65 yo vs. a 95 yo are to be expected.

Part 2 - Safety in the Elderly

This was addressed by the medical officer.

5 SIGNATURES

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.
Senior Reviewer
Division of Pharmaceutical Evaluation -1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

Date

Sally Yasuda, Pharm.D.
Acting – Team Leader
Division of Pharmaceutical Evaluation -1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

5/16/05
Date

Mehul Mehta, Ph.D.
Division Director
Division of Pharmaceutical Evaluation -1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

5/16/05
Date

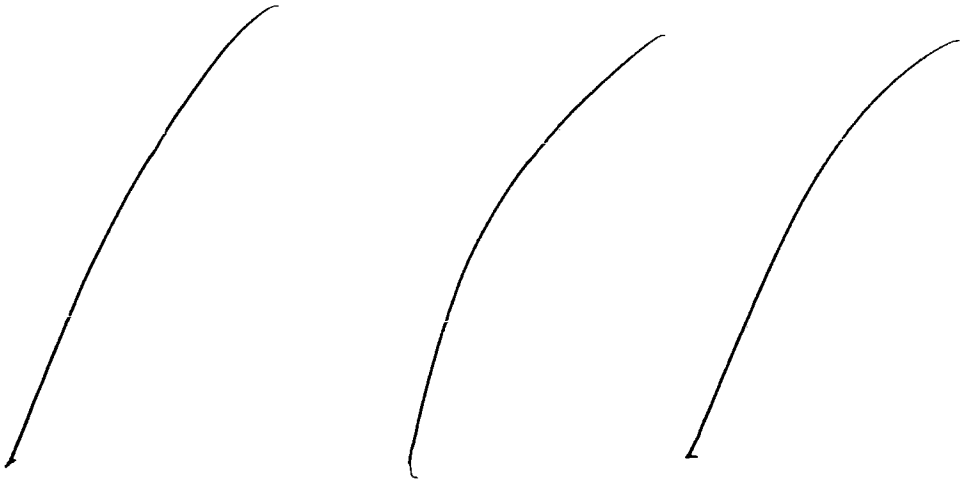
CC List:

NDA 21-726	(orig., 1 copy)
HFD-120	(BatesD, TeleC, OliverT, DubitskyG, LaughrenT, KapcalaL)
HFD-860	(KavanaghR, YasudaS, BawejaR, RahmanA, MehtaM)
CDR	(Barbara Murphy)

6 APPENDICES

Appendix 1 **Proposed D&A Labeling and Summary of OCPB Findings from NDA Major Amendment Review.**

Sponsor's Proposed Labeling for Dosage and Administration



Summary of OCPB Findings Regarding the Major Amendment

[n.b. questions with double asterixes (**) are the major issues identified by OCPB]

Bioequivalence of Clinical and To-Be-Marketed Products

The formulation of the to-be-marketed product is identical to the clinical trial product.

Dose Linearity

Selegiline transdermal systems exhibit linear kinetics over the range of 20 mg to 40 mg per day.

Absorption

The absorption profile is typical of a transdermal system with an initial lag time. Consequently on multiple dosing minimum concentrations occur approximately 1 hour after patch application. Mean Tmax is approximately 5.5 hours and half-life is greater than 24 hours.

Metabolite Kinetics

The concentration time course for desmethylselegiline closely follow those for selegiline, possibly indicating that it is formation rate limited. Whereas the concentration time course for methamphetamine and amphetamine both tend to peak later, indicating possible elimination rate limited kinetics. Alternatively, for amphetamine this may also be due to it being a secondary metabolite possibly with formation rate limited kinetics. Metabolite ratios do not vary by topical application site and are consistent over the dose range of 20 mg qd to 40 mg qd.

** **Relative Bioavailability**

Selegiline exposures after transdermal application, (40 mg / 40 cm^2) are approximately 20 fold higher than after a roughly comparable oral dose (10 mg), and metabolite exposures are approximately 1/3 lower. As selegiline exposures are so high, reliance on safety data from the oral formulation is not appropriate.

Gender

Inspection of the pharmacokinetic data by gender fails to reveal a gender difference.

** **Age**

Examination of dose-normalized concentrations by age reveals a 62.5% increase in selegiline exposure in women from 20 years to 70 years of age, (~1.25% increase per year), and a 25% increase in men, (~0.5% increase per year), Whereas when corrected for dose, exposures to the measured metabolites were essentially unchanged. Due to the increase in selegiline exposure with age all metabolite to selegiline ratios also decline with age.

Body Weight

There is no apparent effect of weight on selegiline pharmacokinetics.

Race

The sponsor has not examined the effect of race on selegiline pharmacokinetics. However, subject demographic data allowed a preliminary examination of the data by race. Examination of these data fails to reveal a clear effect of race on selegiline pharmacokinetics.

** **Risk of Tyramine Reactions – 'Cheese Reaction'**

The sponsor is proposing [redacted] as there is a low risk for tyramine reactions.

There is insufficient data presented to support the conclusion of a low risk for tyramine reactions [redacted], in addition there are several lines of evidence that suggest that tyramine reactions might occur with selegiline transdermal systems. These lines of evidence follow:

Dose Response to Tyramine and MAOI Selectivity

When a surrogate marker for inhibition of whole body MAO-A activity is examined in young males there is a clear dose response, with only 11% mean inhibition of MAO-A at a dose of selegiline TDS 20 mg / 20 cm^2 daily and 50% inhibition at 40 mg / 40 cm^2. Therefore selectivity for MAO-B may be lost as the dose increases through the proposed dosage range of 20 mg to 40 mg daily. In addition, since older individuals have higher selegiline exposures there may not much nearly as much selectivity in older populations with the proposed dosages.

Time Invariance of Tyramine Response

In the original review it was observed that the tyramine pressor dose in challenge studies for the 20 mg system tended to decrease over time (up to 33 days). Consequently the sponsor was asked to repeat the tyramine challenge testing after 60 days of use to provide reassurance that there is not a continuing decline in the pressor dose over time. In addition, the sponsor was told that if the pressor dose showed a continuing decline at 60 days, it would be necessary to also look at later time points.

In the current submission the pharmacodynamic response to a selegiline transdermal dose of 40 mg daily to tyramine challenge doses appears to be time invariant from 1 to 3 months. However, it was noted that the tyramine pressor dose needed to achieve Tyr30, (a tyramine dose needed to raise BP by 30 mmHg), was lower and the tyramine sensitivity factor was higher than noted in the original review with a similar selegiline TDS dosage of 40 mg administered for 10 days. Thus although the pharmacodynamic response does not continue to increase after 30 days, there may be an increase in sensitivity from 10 to 30 days responsible for these disparate observations. Consequently, there does appear to be the potential for sufficient MAOI-A inhibition for a clinically significant tyramine reaction at dosage strengths above the 20 mg patch.

Food - Drug Interaction

Examination of the tyramine response after dosing of selegiline 40 mg TDS for greater than 30 days revealed that the minimum tyramine dose required to elicit a Tyr30 response was 25 mg under fasting conditions and 75 mg under fed conditions. This is consistent with earlier observations that food approximately doubles the amount of tyramine needed to produce a tyr30 response. Since the maximum dose of tyramine in a tyramine rich meal is only 40 mg and since the lowest tyramine dose to produce a tyramine reaction in the presence of food was 75 mg, the probability of a tyramine reaction in clinical practice at first glance seems unlikely. However, it should be noted that this study was performed with young males and the dose of tyramine needed to produce a tyramine reaction is likely much lower in elderly females. This is partly due to pharmacokinetic differences and partly due to loss of arterial elasticity and higher systolic pressure with age. In addition, the study only examined 8 subjects and the determination of tyr30 dose was discrete and not continuous. Thus the risk of a tyramine reaction in clinical practice in response to dietary tyramine is unclear and

** **Contraindication of co-administration with TCAs, other MAOIs, and SSRIs**

** **Application Site Bioequivalence**

Application of the patch to the upper-thigh is bioequivalent to application to the upper-torso. However, application of the patch to the upper-buttock is not bioequivalent to application to the upper-torso and upper thigh, with higher selegiline concentrations after application to the to the-upper buttocks.

No bioequivalency data was provided for application to the upper arm.

According to the medical reviewer, in the pivotal efficacy studies that showed efficacy, (0052, 9806 and 96B), the site of system application was either the upper-torso or upper-arm.

** **Drug Delivery Rate**

The mean delivery rate for the 40 mg patch applied to the torso was 12 mg per day. Assuming linearity the 20 mg and 30 mg patches should deliver approximately 6 mg and 9 mg per day respectively. These rates are recommended for labeling.

Studies from the original submission report similar delivery rates for a 10 mg patch (mean 2.8 mg / 24 hours) although the mean rates for the 20 mg patch in various studies is lower with an overall mean of 5.3 mg / 24 hours for 20 mg over all studies in both submissions, although there's quite a bit of variability. The only study with the overall delivery rate of 5.3 mg (5 mg) / 24 hours with the 20 mg patch would translate to 7.95 mg (or 8 mg) / 24 hours for the 30 mg patch, and 10.6 mg (or 11 mg) / 24 hours for the 40 mg patch.

Thus how to label the amount delivered is somewhat problematic as it's often stated in the literature that loss of selectivity for inhibition of MAO-B occurs at daily oral doses above 10 mg. Consequently, the labeling for Eldepryl® for Parkinsonism states: 'The recommended regimen for the administration of ELDEPRYL is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.'

However, the clinical significance of the 20 fold higher exposure to selegiline with only slightly lower metabolite exposures with the transdermal formulation as compared to similar doses of drug given orally is unclear as the relative contributions of the various species to pharmacologic effect is unknown. As the much higher exposures are to the presumed active agent, this along with dosing near the threshold dose where prescribers expect loss of selectivity indicates that labeling with the higher delivery rate would be prudent.

** **Adhesion**

Dermal adhesion was not appropriately examined and the results likely underestimate the adhesiveness of the patches with clinical use.

Adhesion was examined after application of 20 mg / 20 cm^2 selegiline patches for 10 days to the upper-buttocks, upper-torso, and upper-thigh in site application bioequivalence study P0051.

Approximately 88% - 89% of selegiline 20 mg / 20 cm^2 patches applied to the upper torso exhibited <10% lift with approximately 6 – 7 % of patches becoming detached. Since this study was conducted in an inpatient setting and since larger patches tend to have worse adhesion, the degree of adhesion is expected to be somewhat worse in clinical practice. The degree of adhesion observed is in the lower range that this reviewer expects to see for a patch worn for 24 hours.

** **Dermal Tolerability**

Dermal tolerability was not appropriately examined and the results likely underestimate the dermal intolerability with clinical use.

The dermal tolerability study was an 8 week study conducted in children, 6 to 12 years old, and adolescents, 13 to18 years old. In this study either a low strength, (10 mg / 20 cm^2 or 15 mg / 15 cm^2 depending on patient age), was applied for 8 weeks, or the low strength, (10 mg / 20 cm^2 or 15 mg / 15 cm^2), was applied for 4 weeks followed by a higher strength, (15 mg / 15 cm^2 or 20 mg / 20 cm^2), for an additional 4 weeks. Dermal tolerability with the 30 mg / 30 cm^2 or 40 mg / 40 cm^2 patches was not examined.

It should be noted that the skin of children or adolescents might be more or less sensitive than the skin of adults or the elderly, as each of these 4 groups have different skin characteristics. In addition, the patch sizes used in this study were either 15 cm^2 or 20 cm^2. Since dermal intolerance generally increases with patch size due to occlusion of a greater area, the current study likely underestimates the frequency and degree of cutaneous adverse effects likely to occur with sizes expected to be commonly used in practice, i.e. 30 cm^2 or 40 cm^2.

In spite of these deficiencies, the results can be summarized as follows: Approximately 25% – 45% of children had at least 1 cutaneous adverse event and approximately 10% – 20% of adolescents. All events were mild in intensity and ~10% of events in children required treatment, whereas no adolescents required treatment. Erythema was present in 50% to 75% of cutaneous adverse events, whereas no papules or edema was observed. Swelling or scaling was present in approximately 5% of cases and lesions were palpable in 20% to 25% of cases. Mild itching was present in approximately 30% to 40% of cases, and burning in 5% of cases.

Dissolution Method and Specifications

Changes in the dissolution method as proposed by the sponsor have been adequately justified and the proposed dissolution specifications are acceptable to OCPB.

The method and specifications for the 20 mg / 20 cm^2 strength was previously acceptable to OCPB. However as mentioned above if the sponsor chose to modify either the dissolution method or specifications, (e.g. by addition of higher strengths), then complete information to justify the proposed changes should be submitted.

In addition to 2 additional strengths being added, the volume and apparatus used for the highest strength, (40 mg / 40 cm^2), differs from the other 2 strengths, i.e. 1000 ml and apparatus 6, (rotating cylinder), as compared to 500 ml and apparatus 5, (paddle over disk).

Change in Drug Substance Manufacturing Site

The Change in Drug Substance Manufacturing Site is acceptable to OCPB.

Under submissions N021336 N000 MR 29-Jan-2003 and N021336 N000 BC 13-Mar-2003 the sponsor proposed a change in the drug substance manufacturing site. In response OCPB recommended that the sponsor generate multi-point dissolution profiles as per the accepted method in the original NDA 21-336 and provide F2 calculations for comparison of dissolution profiles of the drug product manufactured using drug substance before and after the site change.

Dissolution data from the batches made with drug substance produced at the two sites were provided and were comparable. F2 calculations were not submitted, but would not alter the conclusions.

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/s/

Ron Kavanagh
5/2/05 11:01:12 AM
BIOPHARMACEUTICS

Sally Yasuda
5/12/05 01:14:50 PM
BIOPHARMACEUTICS

Ron has included your approval of comments sent to Sponsor via project manager on 3/4/05 and therefore has also included you as a signer. Thanks.

Mehul Mehta
5/13/05 12:59:07 PM
BIOPHARMACEUTICS

New Drug Application
Clinical Pharmacology and Biopharmaceutics - Memo to File

NDA:	21-708
Type of Submission	Original NDA
Submission Date	July 31, 2003 October 15, 2003
Related NDA	21-336
Type of Submission of Related NDA:	NDA (AZ) Major Amendment CMC N:030 N(BC) November 7, 2003 (Follow-up to following e-mail) e-mail from Melissa Goodhead [MLG@somersetpharm.com]; Sent: Monday, September 15, 2003 1:42 PM To: KLEIND@cder.fda.gov (C) Briefing Document for May 2, 2002 Meeting with sponsor
Submission Dates of Related NDA:	April 25, 2002 (C) July 31, 2003 September 4, 2003 November 07, 2003 – N(BC)
Generic Name:	Selegiline Transdermal
Formulation:	Transdermal Delivery System
Strengths:	20 mg / 20 cm^2 30 mg / 30 cm^2 40 mg / 40 cm^2
Route:	Topical
Brand Names	EMSAM
Sponsor:	Somerset Pharmaceuticals, Inc. Tampa, FL 33607
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

I. EXECUTIVE SUMMARY

A. Introduction

A major amendment for selegiline transdermal systems was originally submitted under NDA 21-336 on July 31, 2003.

On October 15, 2003 the sponsor submitted this separate NDA (21-708) request for the indication of "Long Term Treatment of Major Depressive Disorder". No new information for review by the office of clinical pharmacology and biopharmaceutics was submitted. All OCPB information is by reference to NDA 21-336 Amendment (AZ) submitted July 31, 2003.

Readers desiring additional information should refer to the OCPB review for NDA 21-336.

II. SIGNATURES

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

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/s/

Ron Kavanagh
6/28/04 06:31:50 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

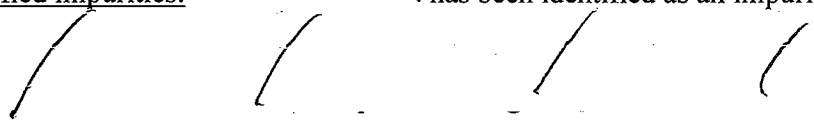
PRODUCT (Generic Name):	Selegiline
PRODUCT (Brand Name):	EMSAM
DOSAGE FORM:	Transdermal System
DOSAGE STRENGTHS:	20 mg, 30 mg and 40 mg
NDA:	21-336 (023)
INDICATION:	Major Depression
NDA TYPE:	Regarding CMC development changes and CMC comments in non-approval letter
SUBMISSION DATE:	1/29/03, 3/13/03
SPONSOR:	Somerset Pharmaceuticals
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

TABLE OF CONTENTS

CMC Development Changes

Through this submission, the sponsor wanted to find out whether the CMC studies conducted are adequate to support the changes. The following CMC development changes have been made:

1. Drug substance manufacturing site change: Somerset's drug substance is manufactured by
   Selegiline base was synthesized at
   Following submission of original NDA and has transfered the full production to include the
   No changes have been made to the manufacturing process and/or equipment.
2. Alternate release liner: Release liner has been changed from to According to the sponsor is very similar in composition to . The s NMT n both. Further according to the Chemist, Dr. Tele, the intent of the release liner is to assist in peel of from the skin and has no release rate controlling properties for the drug itself. This change is therefore deemed minor and dissolution data should be able to address this issue (see recommendations)
3. New identified impurities: has been identified as an impurity.



4. Alternate pouching material supplier

RECOMMENDATION

Please forward the following recommendation to the sponsor:

The sponsor should generate multi-point dissolution profiles as per the accepted method in the original NDA 21-336 and provide F2 calculations for comparison of dissolution profiles of the drug product manufactured using drug substance before and after site change.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D._____

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

/s/

Veneeta Tandon
4/1/03 01:25:47 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
4/1/03 01:38:55 PM
BIOPHARMACEUTICS

EMSAM (Selegiline Transdermal System)
20 mg/20 cm^2 patch
NDA 21-336
Somerset Pharmaceuticals, Tampa, Florida 33607
Indication: Depression
Submission Dates: May 24, 2001, September 25, 2001, January 14, 2002
Received by OCPB: June 5, 2001
Pharmaceutical Division I (HFD-860)
Reviewer: Iftekhar Mahmood, Ph. D.
Team Leader: Ray Baweja, Ph. D.

Recommendation

This submission from Pharmacokinetics and Biopharmaceutics point of view is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. There are no Phase IV commitments.

Iftekhar Mahmood, Ph.D. _____

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

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-336, HFD-120, HFD-860 (Mahmood, Baweja, Mehta), CDR (for Drug-Files) and FOI (HFD-19) files.

Comments to the Medical Reviewers

1. Due to small sample size it is difficult to assess the effect of hepatic impairment, gender and age (especially in the elderly >65 years and children between 6-11 years) on the pharmacokinetics and pharmacodynamics of the STS. Please see if the clinical trials are helpful in identifying the impact of hepatic impairment, gender and age on the safety and efficacy of the STS.

2. In warfarin-selegiline interaction study (study #S9303-P9919), please examine if indeed slight changes in factors VII and X as well as INR values are of any clinical significance.

3. Please also evaluate the Sponsor's [redacted] The Sponsor's statements are as follows:

A. Steady-state treatment with the 20 mg, 30 mg or 40 mg STS increased the mean tyramine sensitivity by a factor of 1.8, 2.4, and 3.5, respectively. Each of these were deemed clinically non-significant since the mean oral tyramine pressor dose for the 20, 30, or 40 mg STS following steady-state dosing was 298 $\pm$105, 210 $\pm$ 88, or 198 $\pm$ 98 mg tyramine, respectively. No subject achieved endpoint (SBP > 30 mmHg above baseline on three consecutive measures) below 75 mg of oral tyramine.

B. The mean oral tyramine pressor dose obtained after 10, 21, and 33 days of treatment with the STS (20 mg/20 cm2) was unchanged (298 $\pm$105 at 10 days; 263 $\pm$119 at 21 days and 204 $\pm$ 86 mg at 33 days), demonstrating the safety of the STS (20 mg/20 cm^2) following chronic daily administration.

Comment

1. The Sponsor's proposed dissolution method and specifications for 20 mg/20 cm2 is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (see page# 21).

Please convey the Comment 1 to the Sponsor.

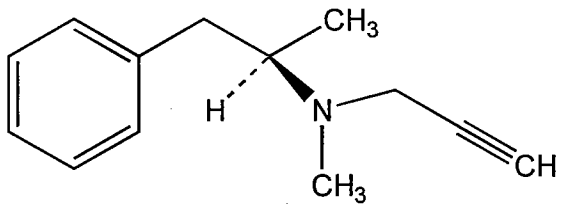
APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENTS

Introduction

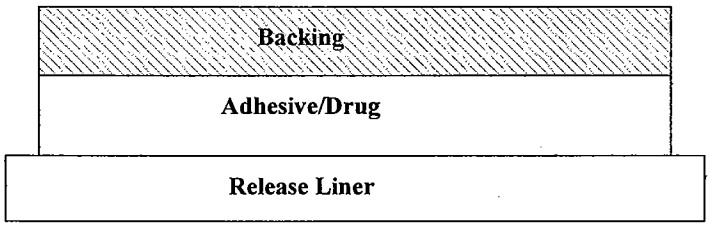
EMSAM™ (selegiline transdermal system) 20mg/20cm^2 is a transdermally administered antidepressant that represents a new generation of monoamine oxidase inhibitor (MAOI). When applied to intact skin, the transdermal system provides controlled selegiline delivery for a sustained antidepressant effect, with selective action on the central nervous system (CNS).

Selegiline base is a colorless to yellow liquid, chemically described as R-(-)-*N*,2-dimethyl-*N*-2-propynylphenethylamine. It has an empirical formula of $C_{13}H_{17}N$ and a molecular weight of 187.28. The structural formula is:



Selegiline Base

The **EMSAM** system is available as a 20mg/20cm^2 transdermal patch that typically delivers 5 mg of selegiline base per day across the skin. Inactive ingredients are acrylic adhesive, ethylene vinyl acetate, [redacted], polyester, polyurethane, and silicon-coated [redacted]



Clinical Pharmacology related to efficacy

Monoamine Oxidase (MAO) is an intracellular enzyme which exists as two isozymes, MAO-A and MAO-B. At lower concentrations, selegiline acts as a selective inhibitor of MAO-B, while at higher concentrations, it inhibits both isozymes. In the CNS, MAO-A and MAO-B play important roles in the catabolism of neurotransmitter amines such as norepinephrine, dopamine, and serotonin, as well as neuromodulators such as phenylethylamine. Inhibition of the activity of one or both of the MAO isozymes alters the brain concentration of these amines.

Although the exact mechanism of the antidepressant action of selegiline transdermal system (STS) or EMSAM is uncertain, inhibition of both MAO-A and MAO-B in brain is believed to be important. In an in vivo animal model used to test for antidepressant activity (Forced Swim Test), selegiline, administered by transdermal patch, exhibited antidepressant properties only at doses that inhibited brain MAO-A and MAO-B activity. The transdermal administration of selegiline provides high, sustained, and targeted systemic levels of selegiline required for inhibition of brain MAO-A and MAO-B and antidepressant activity. In addition, EMSAM avoids first-pass metabolism reducing exposure to its R(-)-amphetamine metabolite.

Chronic transdermal administration of selegiline causes a reduction in the β1, β2-adrenoreceptor and 5-HT2 receptor populations in animal brain tissue. The pharmacological events leading to the "down-regulation" of these brain neurotransmitter receptors are currently unknown but may be secondary to the acute inhibition of brain MAO activity.

MAO is also important in the catabolism of dietary amines (e.g., tyramine) or specific sympathomimetic drugs (e.g., dopamine). Intestinal and hepatic MAO-A provide the vital protection from dietary tyramine (e.g., ingested as cheese, meat and fish products that have undergone fermentation, and some alcoholic beverages) that if absorbed, has the capacity to cause acute hypertension, the so called "cheese reaction". This reaction is associated with the inhibition of MAO-A activity in peripheral tissue sites. Transdermal administration of EMSAM avoids gastrointestinal exposure and provides for targeted inhibition of brain MAO with minimal effects on MAO-A in peripheral tissue sites (i.e., intestine, liver, sympathetic neuron).

Currently it is believed that inhibition of both MAO-A and MAO-B in the brain is necessary for antidepressant activity with selegiline. Since selegiline is a selective MAO-B inhibitor at low concentrations, high plasma (and brain) concentrations are necessary to

achieve MAO-B and MAO-A inhibition. While this goal may be achieved with high-dose oral selegiline HC1 (i.e., 30 to 60 mg/day), a substantial risk of acute hypertension exists following the consumption of dietary tyramine or OTC sympathomimetic decongestants. However, transdermal administration of selegiline minimizes the risk of tyramine-related acute hypertension by reducing the inhibition of intestinal, hepatic and peripheral neuronal MAO-A activity (enzymatic barriers to tyramine and other monoamines) and provides the means for achieving the necessary brain levels for antidepressant therapy. To evaluate the ability of the STS (20 mg/20 cm^2) to inhibit MAO activity in humans, platelet MAO-B was employed as a measure of MAO-B activity and urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) was used as a measure of MAO-A activity. Both are accepted surrogate markers for the activity of the MAO isozymes since platelets contain only MAO-B activity, and MHPG is a principle metabolite of NE, a preferred substrate for MAO-A.

Platelet MAO-B Activity:

Utilizing single STS dosages of 5 mg/10 cm2, 10 mg/10 cm2, and 15 mg/10 cm2, the ability of selegiline to inhibit MAO-B was examined. Time and dose related MAO-B inhibition was noted. The inhibition of MAO-B activity was rapid, with onset noted within 2 hours following application. Maximal platelet inhibition was observed at 24 hours with 73%, 89%, and 100% inhibition, respectively, achieved for the three test doses. The ability to affect platelet MAO activity after multiple dose (7 days) application of the STS was also assessed. Dosages of 5 mg/10 cm2, 10 mg/10 cm2, 15 mg/10 cm2, and 22.5 mg/15 cm2 were studied. Consistent with the previous single dose data, maximal inhibition of platelet activity for the 3 highest dosing groups was achieved by 24 hours (> 90%), with 100% inhibition seen on the last day of application. Platelet MAO activities 14 days after discontinuation were 18%, 57%, 77%, and 78% of pretreatment values for the 4 respective dosages.

Multiple dose treatment with the current STS (20 mg/20 cm^2) demonstrated maximal inhibition ranging from 98 to 100% in all studies conducted. A study employing a dose of STS (30 mg/20 cm^2)produced 99.9% inhibition in platelet activity after 7 days of application. Thus, it appears that multiple dosing with applied STS doses $\geq$ 10 mg results in complete inhibition of platelet MAO activity.

Recovery of Urinary MHPG:

Urinary recovery of MHPG was used as a surrogate marker for MAO-A activity. MHPG is a major metabolite of norepinephrine (NE) and formed only after deamination by MAO. NE is preferentially deaminated by MAO-A in animals and humans. MHPG is

considered an acceptable, non-invasive marker of systemic MAO-A activity throughout the body. However, it must be noted that plasma or urinary MHPG reflects total body or average systemic MAO-A activity and not just that found in the CNS.

MHPG levels were either unaffected or minimally affected following the application of a 5 mg STS or 15 mg STS. The 20 mg STS caused a reduction in MHPG of approximately 21%.

Clinical Pharmacology related to safety

The tyramine challenge studies were conducted with oral tyramine to mimic conditions of real-life exposure in fasted subjects to present the "worse-case-scenario". Administering oral tyramine with food raises the margin of safety of the tyramine pressor dose by a factor of 1.5- to 2.0-fold. Accordingly, the tyramine pressor doses used in these studies provide the most conservative estimate of the safety of the STS when administered concomitantly with dietary tyramine.

Cardiovascular interactions between MAO inhibitor drugs and tyramine (referred to as the "cheese effect") are typically assessed by conducting a tyramine pressor test (also referred to as a tyramine challenge) in healthy subjects in a controlled and monitored in-patient environment. This test involves monitoring of systolic blood pressure (SBP) and heart rate in response to tyramine administration before and after dosing with the MAO inhibitor drug. A minimal rise in SBP of 30 mmHg above baseline is generally considered endpoint, and responses greater than 60 mmHg above baseline are generally terminated by administering alpha- adrenoceptor blocking agents such as phentolamine or labetalol. The minimum dose of tyramine required to elevate SBP 30 mmHg above baseline is referred to as the tyramine pressor dose. The ratio of the presser dose before and after MAO inhibitor drug administration provides a relative index of change in cardiovascular sensitivity to tyramine referred to as the Tyramine Sensitivity Factor (TSF). Accordingly, the TSF value is a measure of the relative safety risk of a hypertensive reaction following concomitant administration of tyramine with a MAO inhibitor drug.

Multiple dose studies with the STS (20 mg/20 $cm^{2)}$ demonstrated a small increase in sensitivity (TSF =1.8) to oral tyramine. This was deemed clinically non-significant since the mean oral tyramine pressor dose in 47 subjects treated to steady-state with the STS (20 mg/20 $cm^{2)}$ was 298 $\pm$105 mg tyramine and no subject achieved endpoint [systolic blood pressure (SBP) $\geq$30 mmHg above baseline on three consecutive measures] below 200 mg of oral tyramine. A tyramine-rich meal is unlikely to contain

more than 40 mg of tyramine.

Steady-state treatment with the 20 mg, 30 mg or 40 mg STS increased the mean tyramine sensitivity by a factor of 1.8, 2.4, and 3.5, respectively. Each of these were deemed clinically non-significant since the mean oral tyramine pressor dose for the 20, 30, or 40 mg STS following steady-state dosing was 298 $\pm$105, 210 $\pm$ 88, or 198 $\pm$ 98 mg tyramine, respectively. No subject achieved endpoint (SBP > 30 mmHg above baseline on three consecutive measures) below 75 mg of oral tyramine.

According to the Sponsor, the mean oral tyramine pressor dose obtained after 10, 21, and 33 days of treatment with the STS (20 mg/20 cm2) was unchanged (298 $\pm$105 at 10 days; 263 $\pm$119 at 21 days and 204 $\pm$ 86 mg at 33 days), demonstrating the safety of the STS (20 mg/20 cm^2) following chronic daily administration.

Comment: The pressor dose is certainly different at day 10 and 33, therefore, the Sponsor's claim that the mean oral tyramine pressor dose obtained after 10, 21, and 33 days of treatment with the STS (20 mg/20 cm2) was unchanged may be inaccurate. However, the clinical significance of these changes needs to be determined by the medical reviewer.

Summary of Clinical Pharmacology and Biopharmaceutics of STS

The clinical pharmacokinetic studies to support the current NDA include bioavailability, mass balance, multiple-dose pharmacokinetics and dose-proportionality studies, effect of age, gender, renal and hepatic impairment, and numerous drug interaction studies. Furthermore, in-vitro drug metabolism, dissolution and patch performance studies have also been conducted. The current clinical formulation STS (20 mg/20cm2) is designed to effectively deliver 4 to 5 mg of selegiline dose over a 24-hour period. The formulation of the pilot batches used in the clinical pharmacology studies is the same as the proposed market formulation. Selegiline is a highly variable drug (%CV = >30).

The Sponsor conducted four double-blind, placebo-controlled randomized clinical trials in adult (18-65 years) patients with depression. The primary efficacy parameter in these controlled clinical trials was the change from baseline in total score of the Hamilton Depression Rating Scale (HAMD), items 1 through 17.

The following is the summary of the clinical pharmacology studies submitted by the Sponsor.

Absorption:

A single application of STS (20 mg/20cm2) resulted in a high and sustained circulating levels of selegiline as compared to oral route. The levels of selegiline metabolites (desmethylselegiline, amphetamine and methamphetamine) were lower by transdermal administration as compared to the oral route of administration. The absolute bioavailability of the STS was 18% (20 mg/20 cm^2). After adjusting the amount of actual dose delivered by the STS (about 5 mg), the absolute bioavailability was 74%. Following a single dose of the STS, the C_{max} was slightly over 2000 pcg/mL and the T_{max} was 18 hours (Study #1). After a single STS (20 mg/20 cm^2) administration, selegiline concentrations in some subjects were measurable till day 7 (Study #2).

Following multiple dose administration (20 mg/20 cm^2 for 10 days), selegiline accumulated in plasma. The accumulation ratio of selegiline, desmethylselegiline, amphetamine and methamphetamine was 3.5, 7.6, 17, and 33.2, respectively (Study #6). Time to reach steady-state is approximately 5 to 7 days (Study #6). Average steady-state trough selegilinc concentrations are approximately 2000 pcg/mL (Study #7).

Distribution:

Selegiline is distributed throughout the body, and rapidly penetrates into the CNS. At physiologically relevant concentrations and pH 7.4, selegilinc exhibits a protein binding of approximately 90%. The absence or presence of the metabolites of selegiline has no impact on its binding properties.

Metabolism:

In vitro:

In vitro studies demonstrated the involvement of a variety of P450 isoenzymes in the metabolism of selegiline. The metabolic profile of selegiline delivered via the STS is qualitatively similar but quantitatively different to that observed after oral administration. Conversion of selegiline to methamphetamine or to N-desmethylselegiline takes place via CYP3A4/5, CYP2B6, and CYP2C9. Subsequent conversion of N-desmethylselegiline to amphetamine involves CYP2B6, CYP3A4/5, and CYP2A6.

The inhibitory effect of selegiline and N-desmethylselegiline on CYP2C9, CYP2C19, CYP2B6, CYP2D6, CYP3A4 and CYP2A6 enzyme activities was assessed in pooled human liver microsomes over a concentration range of 2.5 to 250 microM. Known CYP isoform-selective substrates or inhibitors were used as positive controls.

Selegiline and N-desmethylselegiline caused a concentration-dependent inhibition of CYP2D6 activity at 10-250 microM. Selegiline and N-desmethylselegiline caused a concentration-dependent inhibition of CYP3A4/5 activity at 10-250 microM and 25-250 microM, respectively. CYP2C19 and CYP2B6 activities were inhibited by selegiline and N-desmethylselegiline, but only at high concentrations (100-250 microM). There was no significant inhibitory effect on CYP2A6 or CYP2C9 activities by selegiline or N-desmethylselegiline. Positive control incubations showed moderate to complete inhibition of the appropriate enzyme activities using the CYP isoform-selective substrates and inhibitors.

The cytochrome P450 enzyme activities were inhibited by selegiline and N-desmethylselegiline, at concentrations that were several orders of magnitude higher than are observed in humans at steady-state (0.01 microM) following daily application of the Selegiline Transdermal System (20 mg/20 cm2). Consequently, it would not be expected that the inhibitory effects observed in vitro by selegiline and N-desmethylselegiline would translate into any clinically significant drug-drug interactions.

In Vivo:

In vivo, human metabolism studies reveal the presence of three major metabolites of selegiline. A comparison of AUC ratios across steady-state studies following STS (20 mg/20 cm2) application suggests that methamphetamine (metabolite to parent ratio (M/P) = 2.36) is the principal metabolite followed by amphetamine (M/P = 0.96) and N-desmethylselegiline (M/P =0.55). The contribution of these principal metabolites to the overall antidepressant activity of selegiline delivered via the STS is believed to be minimal. N-Desmethylselegiline is an inhibitor of MAO-B in vitro, although at 1/60 the activity of selegiline (in-vivo activity of desmethyl selegiline is 1/6 of selegiline). Methamphetamine and amphetamine have pharmacological activity in the CNS but their inhibitory potential on MAO is negligible. Selegiline is not metabolized by human skin.

Elimination:

A mass balance study following ^{14}C-selegiline (approximately 300 uCi) accounted for 10.2% and 1.64% total radioactivity in the urine and feces, respectively. A total of 63.4% of the dose was recovered in the dosing supplies (all swabs, applicators, gauze, dressings, and extraneous dressings or cleaning materials that came into contact with the application site, wipes or towels). Overall, 75.3% of radioactive dose was recovered in 7 days (Study #3).

Selegiline undergoes extensive metabolism in humans. Besides liver, other organs may be involved in the metabolism of selegiline. The clearance of selegiline following STS administration is 909 L/hr (CV = 131%) (Study #1). Less than 1% of selegiline dose is excreted unchanged in urine. The elimination half-life of selegiline is about 20 hours (CV = 44%) following STS administration (Study #1).

Dose Proportionality:

Three different STS dose formulations: 5 mg/10 cm^2, 10 mg/10 cm^2, 15 mg/10 cm^2 were used to evaluate dose proportionality of selegiline. The actual dose delivered from 5, 10 and 15 mg patch was 0.60, 2.24 and 4.17 mg/day. Both C_{max} and AUC increased disproportionally with increasing dose for selegiline and its all three metabolites. Non-linearity was noted even based on the actual delivered dose of selegiline from the patch (Study #5).

Effect of Renal Impairment:

The effect of renal dysfunction on the pharmacokinetics of selegiline was studied in three groups of patients (4 per group) with various degrees of renal dysfunction. There were six males and six females in the study. The creatinine clearance in 3 different groups were as follows: Mild group = 50-80 mL/min/1.73 m^2, moderate group = 30-49 mL/min /1.73 m^2, and severe group = <30 mL/min/1.73 m^2. Each patient received a single dose of 20mg/20 cm^2 STS for 24 hours. The results of the study indicated that compared to a historical control group (healthy subjects), the AUC and Cmax of selegiline in patients with renal impairment were lower by 30% to 45%. Due to small sample size and high variability in the pharmacokinetics of selegiline it is however, difficult to assess if indeed compared to a historical control group, the AUC and Cmax of selegiline in patients with renal impairment are lower. It should be noted that the AUC and Cmax values were almost similar among patients with mild, moderate and severe renal impairment and this is not surprising since less than 1% of selegiline dose is excreted unchanged in urine (Study #8).

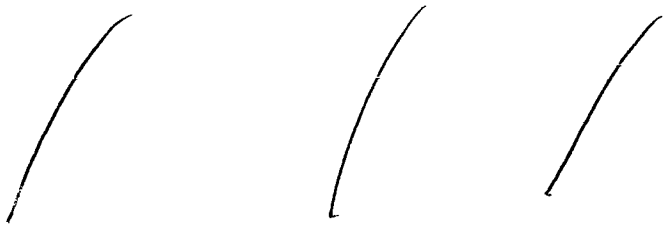
Effect of Liver Impairment:

Effect of liver impairment on the pharmacokinetics and metabolism of selegiline was examined in patients with mild and moderate hepatic impairment. Eight patients with mild (n =1) to moderate (n = 7) liver disease (Child-Pugh classification: A or B) received a single dose of the STS (20 mg/20 cm2). The average apparent dose of selegiline delivered from the STS was 3.96 mg. The results of the study indicated that compared to a historical control group (healthy subjects), the AUC and Cmax of selegiline in patients with hepatic impairment were one-third of the healthy subjects. The metabolite to parent ratio (based on AUCinf) in patients with hepatic impairment for desmethylselegiline, amphetamine and methamphetamine was 0.57, 1.35 and 6.36, respectively. In healthy subjects, this ratio was 0.57, 0.9, and 2.0, respectively. The half-lives of selegiline, desmethylselegiline in patients with hepatic impairment were comparable with healthy subjects but the half-lives of methamphetamine and amphetamine in patients with hepatic impairment were 5 and 2-fold longer as compared to healthy subjects. Due to small sample size it is difficult to conclude if indeed hepatic impairment (mild or moderate) alters the pharmacokinetics of selegiline and its metabolites compared to healthy subjects (Study #9).

Effect of Age:

Elderly:

The pharmacokinetic studies (Studies # 5 and 6) of selegiline STS in elderly subjects (>65 years) indicate that age has no effect on the pharmacokinetics of selegiline. However, due to high variability in the pharmacokinetics of selegiline it is difficult to assess if indeed age has any effect on the pharmacokinetics of selegiline.



Effect of Gender:

Statistically no gender difference was noted in the pharmacokinetics of selegiline and its metabolites. However, the AUC and Cmax were lower in females than males and the difference between the two genders widened with the increasing dose of selegiline (Study #5). At 15 mg dose, the AUC and Cmax in females were 43% and 38%, respectively, lower than the males.

The platelet MAO-B activity decreased with dose. The mean percent inhibition of MAO-B activity in 24 hours for 5, 10 and 15 mg STS was 70 ± 22, 97 ± 3 and 100 ± 0.2, respectively. Based on maximum inhibition (Imax), the females have higher inhibition of MAO-B activity than males at 10 mg and 15 mg selegiline dose, whereas at 5 mg dose, the inhibition of MAO-B activity was higher in males than females. The difference was statistically significant but this difference may not be of any clinical significance.
It should be however, noted that due to small sample size it is difficult to assess the effect of gender in the pharmacokinetics and pharmacodynamics of selegiline.

Pharmacokinetics of selegiline in patients with depression:

In order to evaluate the pharmacokinetics of selegiline via the STS in patients with major depression, trough blood samples were obtained in Phase III efficacy studies

(20 mg/20 cm^2). A total of 177 patients participated in the study. Eighty-eight were on placebo and 89 on STS (20 mg/20 cm^2) for a 6-week period. Blood samples were obtained at baseline and at the week 6 visit in all cases (Study # 23).

The results of this study were comparable to those generated in the Phase I steady state. The average trough concentration in patients, using the 6-week data generated in 73 patients, was approximately 2829 pcg/mL (CV 39 %). For comparison, the average trough concentration 24 hours after the last patch application in 11 male volunteers based on study S9303-P9923 (Study #7 in this review), was 2457 pcg/mL (CV 18%). The overall similarity in the data generated in the major depression patients to that seen in the healthy volunteers for the STS, demonstrates that no major differences exist between the patients and the healthy volunteer population in the pharmacokinetics of transdermally administered selegiline via the STS (20 mg/20 cm2).

Drug Interactions:

The inhibitory potential of selegiline was examined in several in vitro studies using human liver microsomes with concentrations ranging from 2.5 to 250 μM. Both selegiline and N-desmethylselegiline caused a concentration dependent inhibition of CYP2D6 and CYP3A4/5 activities at 10 and 25 μM, respectively. CYP2C19 and CYP2B6 were also inhibited but only at high concentrations (>100 μM). Since the inhibitory effects of selegiline and N-desmethylselegiline occurred at concentrations that were several orders of magnitude higher than concentrations (0.01 μM or 2 ng/mL) seen in vivo in humans with the proposed dose of STS (20 mg/cm^2), it is unlikely that the inhibition observed in these in vitro studies will occur in vivo.

Warfarin:

The individual enantiomers of warfarin exhibit stereospecific metabolism. The S-enantiomer being metabolized by CYP2C9 and the R- enantiomer by CYP3A4. A pharmacokinetic study in 8 volunteers stabilized to INR of 1.5 to 2 failed to show any impact of a 7-day administration of the STS (20 mg/20 cm2) on the pharmacokinetics of individual warfarin enantiomers. However, a change in INR values (0.2 INR unit) was noted. This change may not be of any clinical significance (Study #11).

Alprazolam:

Alprazolam is a substrate for CYP3A4/5 isoenzyme in humans. Its potential to be affected by selegiline or its ability to alter selegiline pharmacokinetics was examined in

12 subjects (10 males and 2 females) following multiple dose. STS (20 mg/20 cm2) or alprazolam (0.5 mg, TID) were administered repeatedly for 7 consecutive days, alone or in combination. Alprazolam decreased the AUC and Cmax of selegiline by 14% and 18%, respectively. Alprazolam did not affect the disposition of selegiline metabolites. This study suggests that it is highly unlikely that selegiline will interact with 3A4 inhibitors (Study #12). The STS did not produce any effect on the pharmacokinetics of alprazolam.

Risperidone:

Risperidone is principally metabolized via CYP2D6. Twelve subjects (6 males and 6 females) received STS (20 mg/20 cm2) or risperidone (1 mg TID) for 7 consecutive days, alone or in combination. Lack of a drug interaction was noted for selegiline and its metabolites or risperidone and its 9-OH metabolite when administered in combination. The results of this study confirmed the in vitro studies that demonstrated the lack of involvement of CYP2D6 in the metabolism of selegiline (Study #13).

Olanzapine:

Olanzapine is metabolized via the CYP1 A2 and CYP2D6 pathways and possibly CYP2A6. A 10-day steady-state study designed in 12 volunteers (5 males and 7 females) examined the potential for a drug interaction between STS (20 mg/20 cm2) and olanzapine 5 mg daily. No change in the pharmacokinetics of either compound was observed (Study #14).

Levothyroxine:

Levothyroxine is a frequently used medicine in patients with major depression and is metabolized by a variety of P450 isoenzymes. Ten subjects (6 males and 4 females) received a single oral dose of levothyroxine (150 μg) on day 1. Subjects then received STS once daily (20 mg/20 cm^2) for 13 consecutive days starting on day 4. On day 14, a single dose of levothyroxine was given in the presence of STS. STS dosing continued till day 16. Levothyroxine single dose pharmacokinetics (as judged by T3 and T4) were unaffected by the STS and levothyroxine did not effect the steady-state pharmacokinetics of selegiline. In this study however, the Tmax of thyroxine was prolonged in the presence of STS. The Tmax of T3 was 43.6 hours (range:1-72 hrs) in the presence of STS as compared to 16.9 hours (range: 1-60 hrs) when thyroxine was given alone. The

Tmax of T4 was 14 hours (range: 2-72 hrs) in the presence of STS as compared to 4.7 hours (range: 1-14 hrs) when thyroxine was given alone (Study #15).

Ibuprofen:

Ibuprofen is a well-known substrate for CYP2C9 isozyme. Since in vitro studies suggested its possible involvement in selegiline's metabolism, the interaction potential of concomitant administration of both of these agents was explored in 10 volunteers (7 males and 3 females). Single doses of ibuprofen (800 mg) were administered alone and after 11 days of the STS (20 mg/20 cm2) administration. The pharmacokinetics of ibuprofen before and after chronic STS administration was unaltered. Ibuprofen, though administered as a single dose, did not produce any effect on the pharmacokinetics of selegiline. This finding may indicate the lack of involvement of CYP2C9 in humans (Study #16).

Alcohol:

The effect of chronic administration of selegiline (once daily (20 mg/20 cm^2) for 10 consecutive days) was studied on an acute dose of alcohol in 15 male volunteers. Alcohol was given in the form of commercially available Everclear (0.75 g/kg) mixed in grape juice (20% v/v) and was ingested before and after the administration of the STS. Selegiline did not alter the pharmacokinetics of alcohol or vice versa. The combination of the STS and alcohol did not produce any significant effect on memory, learning, psychomotor performance as compared to when alcohol was given alone (Study #17).

Pseudoephedrine:

Drug interactions between sympathomimetic agents and a variety of MAO inhibitors have been previously observed. Given the presence of pseudoephedrine in a wide variety of OTC cough/cold medications, an interaction study evaluated the pharmacokinetics and pharmacodynamics effects of chronic administration of selegiline on pseudoephedrine. In order to determine baseline pharmacokinetics and blood pressure, a single 60 mg dose of pseudoephedrine was administered on Day 1 followed by 60 mg TID on Days 2 and 3 (9 males and 3 females). A 10-day regimen of STS (20 mg/20 cm2) was then initiated. On the last three days of treatment, the pseudoephedrine regimen was repeated. Treatment with the STS had no clinically meaningful effects on either the pharmacokinetics or pharmacodynamics of pseudoephedrine. The appropriate

use of pseudoephedrine containing products are not likely to produce any clinically meaningful effect in patients treated with the STS (20 mg/20 cm2) (Study #18).

Ketoconazole:

Ketoconazole is a potent inhibitor of the CYP3A4 isozyme. Ten healthy volunteers (5 males and 5 females) received STS (20 mg/cm^2) once daily for 7 days. From day 8 to 14, subjects received STS with ketoconazole (200 mg daily). Ketoconazole did not alter the pharmacokinetics of STS. Ketoconazole, however, increased the AUC of selegiline metabolites by 30% (Study #19).

Carbamazepine:

Carbamazepine is an enzyme inducer. The effect of 200 mg carbamazepine twice daily for 14 days was evaluated in 10 subjects (7 males and 3 females) on the single dose pharmacokineties of STS (20 mg/20 cm2). Carbamazepine increased the AUC and Cmax of STS by 92% and 71%, respectively. The AUC of desmethylselegiline was lower by 28% but amphetamine and methamphetamine AUCs increased by 100% and 52%, when selegiline was given with carbamazepine as compared to selegiline given alone. The results of the study are rather surprising as carbamazepine is an enzyme inducer and it should decrease selegiline levels. The STS did not alter the pharmacokinetics of carbamazepine (Study #20).

Cocaine:

A single dose of cocaine (0.5 mg/kg over 10 minutes followed by 2 mg/kg over 4 hours) was intravenously infused to experienced, nondependent cocaine users (n =12; 11 males and 1 female). STS (20 mg/20 cm^2) was administered on day 4 and continued through day 12. The second cocaine infusion took place 2 hours after the administration of STS on day 11. The results of the study indicated that the STS produced no effect on the pharmacokinetics of cocaine or its metabolite. Single dose cocaine did not effect the trough levels of selegiline and desmethylselegiline. Pharmacodynamic parameters (blood pressure, heart rate, respiration rate) were also not effected by the STS (Study #21).

Phenylpropanolamine:

In order to evaluate the interaction potential of selegiline with other sympathomimetics, a study was conducted to evaluate the effects of chronic administration of STS (20 mg/20 cm2) on the pharmacokinetics and pharmacodynamics

of phenylpropanolamine in 11 healthy male volunteers. A single 25 mg dose of phenylpropanolamine was administered on Day I followed by a multiple dose of 25 mg every 4 hours for 6 additional dosages. A 9-day regimen of STS was then initiated. On the last two days of STS treatment, the phenylpropanolamine regimen was repeated. Chronic administration of the STS produced no effect on the pharmacokinetics of phenylpropanolamine (Study #22). Effect of phenylpropanolamine on the STS was not evaluated.

Analytical Method:

For the simultaneous quantification of selegiline, N-desmethylselegiline, amphetamine, and methamphetamine, the assay is [redacted] extraction procedure coupled with a high performance liquid chromatographic mass spectrometric detection. The assay utilizes [redacted] as an internal standard (IS). All the assays demonstrated acceptable within and between day accuracy and precision. The lower limit of quantification for selegiline, N-desmethylselegiline, amphetamine and methamphetamine was [redacted] respectively. The stability of extracted specimens for re-injection was at least 48 hours.

Dissolution:

The Sponsor's proposed dissolution method for the STS is as follows:

Apparatus: Apparatus 5 (paddle over disk)
Medium: 0.1 M Phosphate buffer, pH = 5.0
Volume: 500 mL
Temperature: 32^0C
Paddle speed: 50 rpm
Specification:

1 hour: [redacted] (range: [redacted]
4 hours: [redacted] (range: [redacted]
8 hours: [redacted] (range: [redacted]
24 hours: NLT [redacted]

The effect of pH and paddle speed on drug release were also studied by the Sponsor. The data indicate that the dissolution of the STS is not affected between pH 3 to 6, and

various paddle speeds. Based on the results of pivotal biobatches, the specification time points and their range appears appropriate.
Sponsor's proposed dissolution method for STS is acceptable to the FDA.

Formulation:
The proposed STS market product consists of the following components:
1. Backing film

2. Drug/Adhesive Matrix (selegiline base/acrylic adhesive .

3. Release liner
4. The STS is packaged in a paper/foil/ pouch stock.

The STS used in all clinical trials employed a pigmented backing film. Recently, non-pigmented backing material has been used resulting in a translucent patch.

. The STS delivered approximately 5 mg of selegiline (25% of the label claim) over a 24-hour dosing period. The formulation of the pilot batches used in the clinical pharmacology studies is the same as the proposed market formulation.

Conclusion:

STS (20 mg/20 cm2) has been shown to be an effective delivery system for maintaining high and sustained plasma concentrations of selegiline as compared to the oral route of administration. No qualitative differences were noted in selegiline metabolism between transdermal and oral administration. The transdermal route effectively minimized the formation of selegiline metabolites while increasing its circulating concentrations. The STS (20 mg/20 cm2) was found to be acceptable with respect to adhesion characteristics and irritation. The STS delivered approximately 5 mg of selegiline over a 24-hour dosing period (25% of the label claimed dose). No significant differences were noted in various disease states or sub-populations or between depressed patients and various healthy volunteer populations. Interaction studies demonstrated that selegiline did not alter the pharmacokinetics of a wide variety of drugs studied in this NDA.

Answers to the Questions as they Appear in Section IV in GRP

A. General Attributes:

As its HCl salt (33 mg/mL), selegiline is water soluble. It has a partition coefficient (octanol/water) of 3.4, a pKa of 7.5 and a molecular weight of 187.5. Selegiline readily permeates through skin. Generally, 20 mg/20cm^2 patch delivers approximately 5 mg dose over 24 hours. Selegiline is not metabolized by skin. Due to its favorable physico-chemical properties, selegiline transdermal system may be beneficial for a variety of CNS disorders. Though selegiline is given orally with levodopa for the management of Parkinson's disease, the selegiline transdermal system (20 mg/20 cm2) is intended for the treatment of depression.

B. Clinical Pharmacology:

Selegiline is an irreversible selective inhibitor of Monoamine Oxidase (MAO). As 10 mg oral dose, selegiline is a potent inhibitor of platelet MAO-B activity and within 24 hours inhibits >95% MAO-B activity. At the higher doses (>40 mg), selegiline looses its selectivity and MAO-A inhibition also begins. With the transdermal selegiline, the concentrations of the parent compound are relatively higher than the oral dose. As a result MAO-A inhibition occurs though it is not known if indeed MAO-A inhibition is one of the mechanisms through which an antidepressant works.

Selegiline is the active moeity in plasma which can be measured at picogram levels using LC MS/MS analytical method. The three metabolites of selegiline are: desmethylselegiline, amphetamine and methamphetamine which can also be simultaneously measured by the above analytical method. Desmethylselegiline has negligible MAO inhibitory potential whereas amphetamine and methamphetamine do not inhibit MAO.

The pharmacokinetics of selegiline are nonlinear over the dose range of 0.5 to 1.5 mg/cm2 (0.85 to 6.13 mg delivered dose). Following multiple dosing there is accumulation of selegiline in the body (3.5 fold increase as compared to a single dose).

Though complete inhibition of platelet MAO-B activity occurs within 24 hours, the clinical benefit does not start immediately or parallel MAO inhibition. It may take weeks before any real clinical benefit is observed. There are no unresolved dosing administration issues.

Based on the trough levels of selegiline between healthy volunteers and the patients with depression, the pharmacokinetics of selegiline were comparable. Selegiline is extensively metabolized and is a highly extracted drug.

Whether given by oral route or transdermally, selegiline is a highly variable drug. Absorption varies widely among subjects, which results in high variability of this drug.

B. Intrinsic Factors:

The results of the study in patients with renal impairment indicated that compared to a historical control group (healthy subjects), the AUC and Cmax of selegiline in patients with renal impairment were lower by 30 to 45%. Due to small sample size and high variability in the pharmacokinetics of selegiline it is difficult to assess if indeed compared to a historical control group, the AUC and Cmax of selegiline in patients with renal impairment are lower. It should be noted that the AUC and Cmax values were almost similar among patients with mild, moderate and severe renal impairment (less than 1% of selegiline dose is excreted unchanged in urine).

The results of the study in patients with hepatic impairment indicated that compared to a historical control group (healthy subjects), the AUC and Cmax of selegiline in patients with hepatic impairment were almost one-third than the healthy subjects. Due to small sample size it is difficult to conclude if indeed hepatic impairment (mild or moderate) alters the pharmacokinetics of selegiline and its metabolites compared to healthy subjects.

Age (elderly vs young) has no effect on the pharmacokinetics of selegiline.

Statistically, though no gender difference was noted in the pharmacokinetics of selegiline and its metabolites, the AUC and Cmax were lower in females than males and the difference between the two genders widened with the increasing dose of selegiline. At 15 mg dose, the AUC and Cmax in females were 43% and 38% lower than the males, respectively.

No information is available on the pharmacodynamics of selegiline on age, hepatic or renal impairment. In females, MAO-B activity was found to be slightly higher than males after STS administration (10 and 15 mg dose) but it may not be of any clinical significance.

D. Extrinsic Factors:

The effect of chronic administration of selegiline (once daily (20 mg/20 cm^2) for 10 consecutive days) was studied on an acute dose of alcohol in 16 volunteers. Alcohol was given in the form of commercially available Everclear (0.75 g/kg) mixed in grape juice (20% v/v) and was ingested before and after the administration of the STS. Selegiline did not alter the pharmacokinetics of alcohol. The combination of STS and alcohol did not produce any significant effect on memory, learning, psychomotor performance as compared to when alcohol was given alone.

The in-vitro drug metabolism study indicated that CYP2B6, CYP2C9 and CYP3A/5 appeared to be the major contributing CYP enzymes in the formation of desmethylselegiline and methamphetamine from selegiline with CYP2A6 having a minor role. CYP2A6, CYP2B6 and CYP3A4/5 appeared to contribute to the formation of amphetamine from N-desmethylselegiline (either on direct incubation or following formation from selegiline).

Selegiline and N-desmethylselegiline caused a concentration-dependent inhibition of CYP2D6 activity at 10-250 microM. Selegiline and N-desmethylselegiline caused a concentration-dependent inhibition of CYP3A4/5 activity at 10-250 microM and 25-250 microM, respectively. CYP2C19 and CYP2B6 activities were inhibited by selegiline and N-desmethylselegiline, but only at high concentrations (100-250 microM). There was no significant inhibitory effect on CYP2A6 or CYP2C9 activities by selegiline or N-desmethylselegiline. Positive control incubations showed moderate to complete inhibition of the appropriate enzyme activities using the CYP isoform-selective substrates and inhibitors.

The cytochrome P450 enzyme activities were inhibited by selegiline and N-desmethylselegiline, at concentrations that were several orders of magnitude higher than are observed in humans at steady-state (0.01 microM) following daily application of the Selegiline Transdermal System. Consequently, it would not be expected that the inhibitory effects observed in vitro by selegiline and N-desmethylselegiline would translate into any clinically significant drug-drug interactions.

F. Analytical Method:

For the simultaneous quantification of selegiline, N-desmethylselegiline, amphetamine, and methamphetamine, the assay is a ⁀ extraction procedure

coupled with a high performance liquid chromatographic mass spectrometric detection. The assay utilizes [redacted] as an internal standard (IS). All the assays demonstrated acceptable within and between day accuracy and precision. The lower limit of quantification for selegiline, N-desmethylselegiline, amphetamine and methamphetamine was [redacted] respectively. The stability of extracted specimens for re-injection was at least 48 hours.

G. Dissolution:

Sponsor's proposed dissolution method for the STS is acceptable to the FDA. Dissolution method for the STS is robust and the data indicate that the dissolution of the STS is not affected between pH 3 to 6, and various paddle speeds.

Study #1

Title: Single dose pharmacokinetic comparison of transdermal selegiline 20 mg patches versus intravenous infusion (10 mg/24 hours) versus oral (10 mg) administration to healthy male volunteers (Study # S9303-P9809).

This was a single-dose, single-center, randomized, open-label, three way crossover study. Twelve healthy male subjects (21 to 40 years of age) took part and completed the study. Subjects received a single dose of transdermal selegiline system (STS), 20 mg/20 cm^2 or intravenous infusion (10 mg/24 hours) or oral dose (2x5 mg selegiline capsules). There was a washout period of 8 days between the treatments. Blood and urine samples were collected till 96 hours for determination of selegiline and its metabolites.

The results of the study indicated that selegiline is extensively metabolized by oral administration as compared to IV or STS route of administration. Maximum plasma concentrations were observed following IV administration, followed by STS and oral administration. Selegiline plasma concentrations were detectable only in 4 subjects beyond 12 hours following oral administration whereas selegiline concentrations were detectable till 96 hours following patch (in 7 subjects) and IV (in all subjects) administration.

The amount of delivered dose by STS patch was 4.78 mg. The absolute bioavailability of selegiline following oral administration and STS was 4.4% and 18%, respectively. After adjusting the amount of dose delivered by STS (4.78 mg) the absolute bioavailability of STS was 74%.

The C_{max} of selegiline following oral administration and by STS was slightly over 2 ng/mL and the time to reach this concentration was about 1 hour and 18 hours, respectively. The systemic clearance of selegiline was close to liver blood flow but the apparent clearance following oral administration and by STS was many times higher than the liver blood flow (STS = 909 L/hr, oral = 24780 L/hr). The elimination half-life of selegiline following IV, STS and oral administration was 25,20 and 9 hours. Less than 1% drug was excreted unchanged in urine.

Irrespective of the route of administration, quantitatively L-methamphetamine was major metabolite followed by L-amphetamine and N-desmethylselegiline. The pharmacokinetic parameters have been summarized in the following Table.

Pharmacokinetic Parameter	N=12	Selegiline		N-desmethylselegiline		L-amphetamine		L-methamphetamine	
		Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
$AUC_{(0-inf)}$ (pg*hr/mL)	Trans	46162.29	61	22959.86	68	42692.30	50	93088.03	59
	IV	106023.5	24	54576.67	42	85821.85	22	204048.3	25
	Oral[a]	4537.36	124	67684.55	44	115842.6	15	289197.3	19
$AUC_{(0-t)}$ (pg*hr/mL)	Trans	44375.79	61	21242.99	70	38910.63	64	85639.23	59
	IV	102470.3	24	52204.79	43	77684.52	22	190722.1	24
	Oral	4537.36	124	67684.55	44	115842.6	15	289197.3	19
$AUC_{(0-24)}$ (pg*hr/mL)	Trans	29425.87	66	11292.99	76	7448.37	73	24130.96	67
	IV	68220.14	31	26763.45	42	17610.52	24	55839.99	23
	Oral	4365.11	123	63635.56	42	68244.75	12	195752.1	13
C_{max} (pg/mL)	Trans	2162.3	78	791.4	67	795.8	56	2171.3	52
	IV	4570.3	23	1833.3	35	1900.3	25	4972.0	20
	Oral	2222.1	92	22992	35	3740.9	12	13150.3	12
T_{max} (hr)	Trans	18.38	37	19.58	26	29.17	4	27.5	15
	IV	19.90	16	21.32	19	28.17	7	26.83	15
	Oral	0.86	31	0.88	28	5.85	44	2.54	57
T_{lag} (hr)	Trans	1.58[a]	57	5.01	56	9.34	62	6.01	53
	IV	1.00[a]	1	1.34	37	5.5	16	3.17	33
	Oral	0.4[a]	33	0.31	36	0.61	21	0.53	15
$T_{½}$ (hr)	Trans	20.1	44	15.07	52	25.33	22	20.47	23
	IV	24.64	26	18.82	27	23.52	26	20.69	23
	Oral	8.65	148	8.73	42	15.48	15	14.24	19
K_{el} (1/hr)	Trans	0.05	102	0.063	62	0.029	23	0.036	25
	IV	0.03	28	0.04	28	0.032	30	0.035	23
	Oral	0.344	95	0.097	52	0.046	16	0.051	21
MRT[b] (hr)	Trans	26.11	17	30.37	21	49.34	22	43.64	13
	IV	27.49	16	31.35	14	49.05	13	42.05	11
	Oral	2.58	78	5.64	38	23.21	11	19.4	13
CL (L/hr)	Trans	909.11	131	-	-	-	-	-	-
	IV	84.56	31	-	-	-	-	-	-
	Oral	24779.75	207	-	-	-	-	-	-
CL_F (L/hr)	Trans	0.6393	171	0.7742	45	7.329	35	8.1503	32
	IV	0.4582	62	0.9216	30	8.0425	26	8.7431	23
	Oral	0.9346	158	0.9821	64	7.6364	25	7.5873	24
%Fe	Trans	0.0665	45	0.351	58	7.184	40	17.569	40
	IV	0.5501	57	0.616	41	11.078	20	26.199	25
	Oral	0.0191	99	0.740	53	14.408	21	32.886	28
AUCI M/P	Trans	-	-	0.55	40	0.96	40	2.39	48
	IV	-	-	0.51	31	0.83	21	2	27
	Oral[c]	-	-	86.07	160	320.56	206	903.05	231
AUCT M/P	Trans	-	-	0.52	38	0.74	28	2.28	46
	IV	-	-	0.5	32	0.78	22	1.94	26
	Oral	-	-	86.07	160	320.56	206	903.05	231

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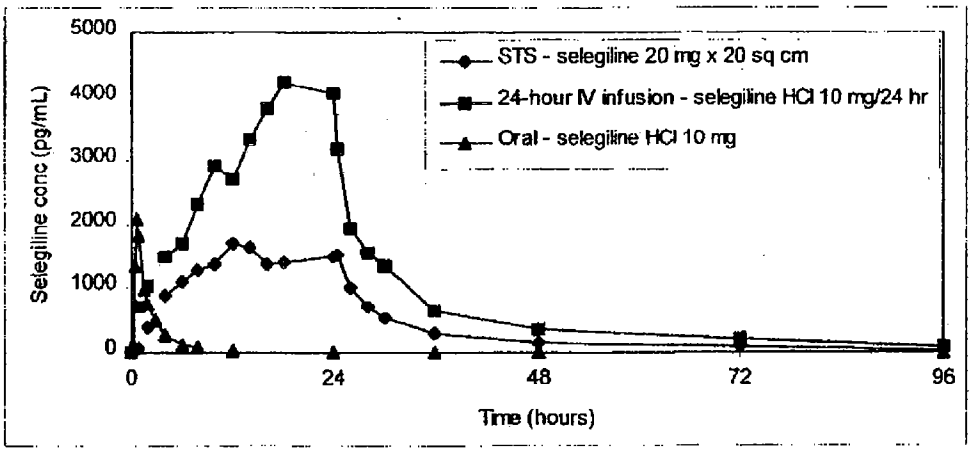

Figure 11. **Mean Selegiline Plasma Concentration-Time Profiles in Healthy Male Volunteers (N=10) after Single Dose Administration of STS (20 mg/20 cm^2), Intravenous Infusion (10 mg/24 hr) and Oral (10 mg) Selegiline HCl**

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Study #2

Title: A preliminary single dose study to examine the duration of selegiline delivery from the 20 mg selegiline transdermal system in healthy volunteers (Study # S9303-P9808).

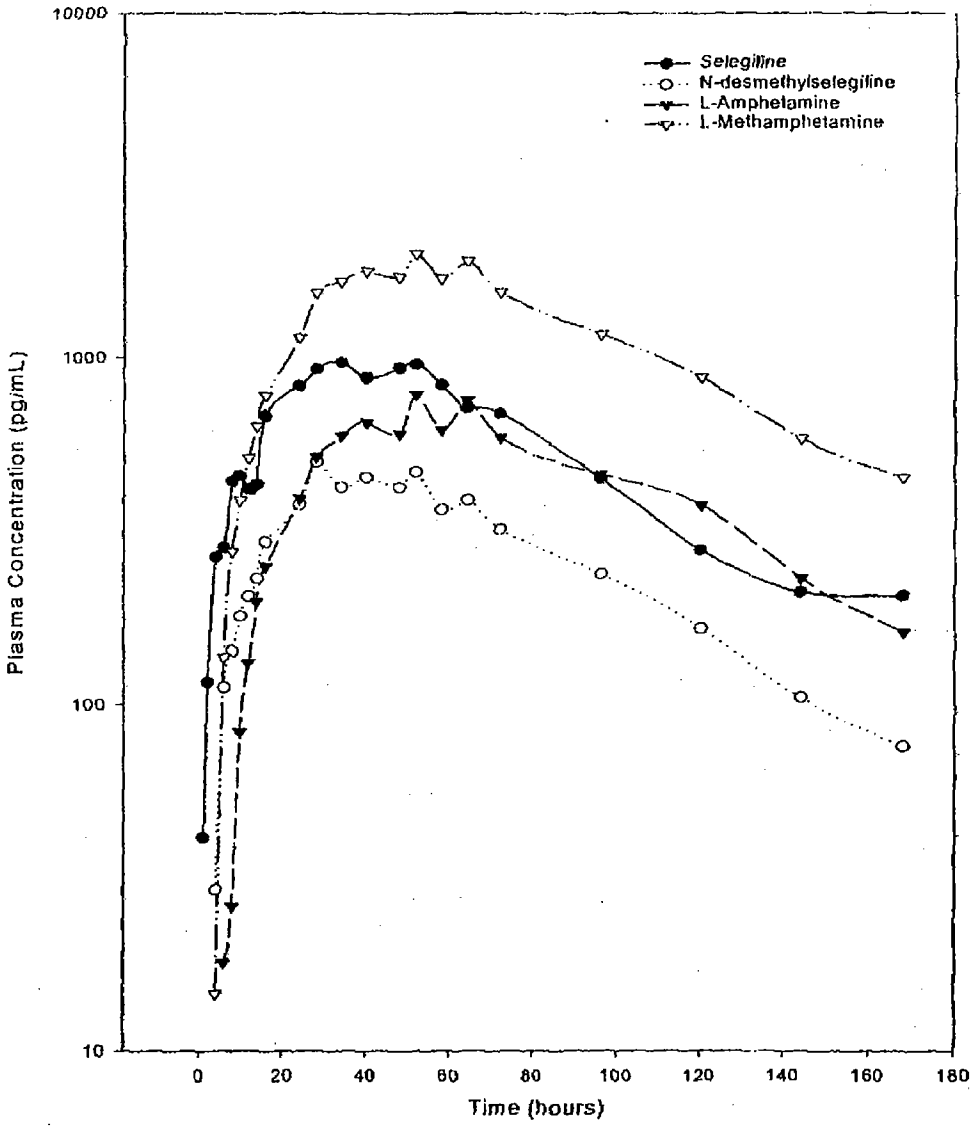
This was a single center, single dose, open-label study to evaluate the ability of the 20 mg STS to deliver drug beyond 24 hours in healthy subjects. Six male and four female healthy subjects (19 to 41 years) took part in this study. Each subject received 20 mg selegiline (20 mg in 20 cm^2 patch). The patch was taped during the course of the study (7 days) to ensure contact with the skin. Blood sample were taken at regular intervals till 168 hours for determination of selegiline, desmethylselegiline, methamphetamine and amphetamine.

All 10 subjects completed the study. The amount of drug released from the patch ranged from [redacted] mg (mean = 12.8 ± 1.54 mg). The Cmax and Tmax for selegiline were 1128 pg/mL (%CV = 36) and 41 hours (%CV = 49), respectively. L-methamphetamine concentrations were the highest among the three metabolites, followed by amphetamine and desmethylselegiline. Selegiline was cleared rapidly from the circulation (CL = 158 liters/hr). The study indicated that transdermal delivery of selegiline is possible beyond 24 hours. In fact, selegiline concentrations were detectable in some subjects even on day 7. Another feature of STS was that multiple peaks of selegiline and its metabolites were observed over the span of seven days. The Pharmacokinetic parameters of selegiline and its metabolites have been summarized below:

Pharmacokinetic Parameter	Selegiline	N-desmethylselegiline	L-methamphetamine	L-amphetamine
AUCT [pg*hr/mL]	86228.7 (36)	41274.2 (54)	181913.8 (42)	68401.9 (30)
AUCT metab/parent Ratio	-	0.5 (30)	2.1 (21)	0.8 (19)
CL (L/hr)	158.5 (29)[a]	[b]	[b]	[b]
C_{max} [pg/mL]	1128.1 (36)	538.6 (55)	2121.1 (37)	809.4 (28)
MRT [hr]	65.2 (19)	64.8 (21)[c]	73.6 (12)[c]	76.0 (13)[c]
T_{lag} [hr]	1.4 (37)	5.4 (18)	6.4 (20)	10.6 (24)
T_{max} [hr]	40.6 (49)	34.6 (28)	52.8 (13)	55.2 (11)

[a] n=9 subjects since Subject 06 lost his STS and apparent dose could not be calculated.

Figure 5.1. Mean Plasma Concentration Time Profiles (Semi-Log) for Selegiline and Its Metabolites (All Subjects)



Study #3

Title: Single dose pharmacokinetic/metabolism study of transdermal 14C-selegiline HCl in healthy male volunteers (Study# S9303-P9810).

This was a single-center, single dose, open-label study in 6 healthy male subjects between 24 and 41 years of age. Each subject received one single application of 14C-selegiline HC1 (approximately 300 uCi) topically over a 20 cm^2 area on the upper torso. Blood samples were collected at regular intervals till 168 hours. Seven, 0- to 24-hour urine samples were collected on Days 1 to 7. Fecal samples were also collected during the 0- to 168-hour study period. Both urine and fecal samples were assayed for determination of total radioactivity, total conjugates (sulfate and glucuronide), selegiline, and its metabolites. Skin biopsy samples, for determination of total radioactivity, were collected pre-dose and at 24.5, 48, 96, and 168 hours post-drug application. All swabs, applicators, gauze, dressings, and extraneous dressings or cleaning materials that came into contact with the application site,wipes or towels, on Days I to 8 were collected, for determination of total radioactivity.

Selegiline concentrations were measureable only till 36 hours. Mean Cmax for selegiline was 828 pg/mL and occurred at 1.2 hours after the administration of dose. Half-life of selegiline was about 9 hours. The following Table summarizes the pharmacokinetic parameters of selegiline and its metabolites.

Parameters	Selegiline	Desmethylselegiline	Methamphetamine	Amphetamine
C_{max}	828 (42)	239 (39)	695 (20)	228 (20)
T_{max} (hrs)	1.2 (59)	4.3 (54)	13 (41)	15 (40)
$AUC_{(0\text{-inf})}$	6124 (29)	3386 (31)	22721 (18)	13481 (59)
CL (l/hr)	1849 (31)	NA	NA	NA
T1/2 (hrs)	9 (55)	11 (84)	16 (31)	27 (68)
%Fe	0.02 (33)	0.03 (47)	2.7 (17)	0.88 (23)

The units of Cmax and AUC are pcg/mL and pcg*hr/mL. NA = Not applicable
Fe = Fraction of dose excreted unchanged in urine.

Total radioactivity excreted in the urine and feces accounted for 10.2% and 1.64%, respectively. In addition, a total of 63.4% of the administered dose was recovered

in the selected dosing supplies (swabs, applicators, gauze, dressings, cleaning materials such as wipes and towels). Overall, about 12% of the administered radioactive dose was recovered in urine and feces in 7 days.

The metabolite-to-parent compound AUC(0-inf) ratios indicate that methamphetamine was the major metabolite, followed by amphetamine and N-desmethylselegiline. The metabolite-to-parent ratios were approximately 0.55, 1.73, and 3.81 for N-desmethylselegiline, amphetamine, and methamphetamine, respectively.

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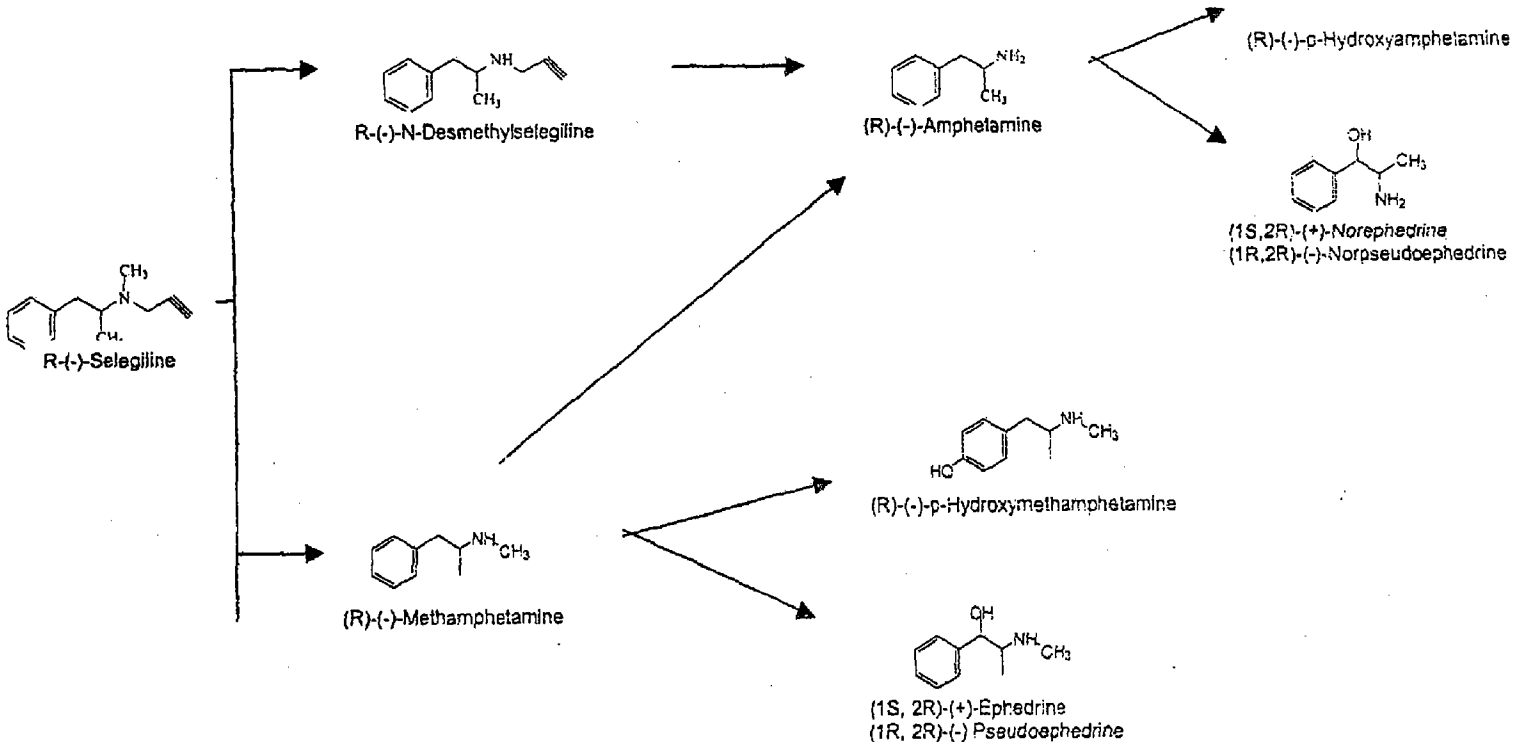
Figure 5.2. Potential Pathways of Selegiline Metabolism



Study #4

Title: Pharmacokinetic evaluation and wearability of three different selegiline transdermal system (STS) formulations (0.5, 1.0, and 1.5 mg/cm^2 selegiline) in healthy males (Study# S9303-030-95B).

The objectives of this study were to determine the disposition characteristics of selegiline, amount of dose delivered from the patch and wearability of the patch following the application of three different STS formulations (0.5 mg/cm^2, 1.0 mg/cm^2 and 1.5 mg/cm^2) in healthy adult male volunteers. The ST'S used in this study were 10 cm^2 in size. This study was a parallel-group study. Twenty-four healthy male subjects (19 to 36 years of age) were randomly assigned to one of the two groups. Twelve subjects randomized to Group A (referred to as pharmacokinetic group) received one of the three STS doses (4 subjects in each dose group). Similarly, the 12 subjects randomized to Group B (referred to as wearability treatment group) were also divided into 4 subjects each dose group. Group A subjects were studied after one 24 hour STS application whereas Group B subjects received two 24 hour STS applications over a 48 hour study period. Group A subjects were restricted from any strenuous or athletic activities on the day of STS application and were not permitted to shower, touch or alter the applied STS in any way until removal. In contrast, the wearability of the STS was assessed in group B subjects under varying conditions. Group B subjects were required to complete a 20 minute brisk walk sufficient to achieve noticeable perspiration 6 hours post STS application. Wearability was assessed immediately prior, immediately after and 30 minutes after the completion of this walk. Group B subjects were required to take a 10 minute shower 12 hours post application, avoiding any contact with soap or any direct manipulation of the STS. Wearability was assessed immediately prior to, immediately after and 30 minutes after the shower. STS wearability was characterized by assessing patch lift 5-point scale, residual adhesiveness (4-point scale) and local skin reactions (5-point scale). Blood samples were collected at time 0,1, 2, 4, 6, 8, 10, 12, 16, 24.26 30, 36, 48 72 and 96 hours for subjects in group A. For subjects in group B, blood samples were collected at time 0, 12, 24, 48 and 72 hours after the STS application. Patches were designed to deliver approximately 2, 4 or 6 mg of selegiline over a 24-hour period. The actual dose delivered from the patch is summarized in the following Table.

Table 1. Amount of Selegiline Dosed from each Selegiline Transdermal System (STS) Formulation

STS	Selegiline Dosed in mg from STS 24-hour application		
	Expected 24-hour dose (mg)	Group A Subjects (n=4)	Group B Subjects (n=8)*
0.5mg/cm^2(10cm^2)	2	0.85 (0.06)	1.28 (0.3)
1.0mg/cm^2(10cm^2)	4	3.13 (0.70)	3.04 (0.3)
1.5mg/cm^2(10cm^2)	6	5.53 (1.10)	6.13 (0.9)

Data presented as mean (+ SD)
*4 subjects each received 1 STS on 2 consecutive days

Selegiline absorption was rapid with the 10.0mg/10cm^2 and 15.0 mg/10cm^2 STS. The amount of selegiline observed in the plasma of subjects who received the 5 mg/10 cm2 STS was very low, approaching the lower limit of quantification. In addition, no selegiline metabolites were observed in the plasma of any subject who received the 5.0mg/10cm^2 STS. By contrast all metabolites and selegiline were within the detectable limits in plasma of subjects dosed with the 10.0mg/10cm^2 and 15.0mg/10cm^2 STS. The following Table summarizes the pharmacokinetic parameters following the administration of 3 different doses of STS. The apparent increases in Cmax and AUC observed in this study are non-proportional with respect to either the theoretical delivered doses (i.e., 2, 4 or 6 mg) or the

Table 2. Comparative Elimination Half-Life, Maximal Plasma Concentration and Area Under the Curve Evaluations after Application of Three Different Selegiline Transdermal System (STS) Formulations

Compound+	T ½	C_{max} (pg/mL)	C_{max} Ratio C/B	AUC_{0-t} (pg•hr/mL)	AUC Ratio C/B	AUC_{0-inf} (pg•hr/mL)	AUC Ratio C/B
Selegiline							
A (0.5mg/cm^2 x 10cm^2)		18.3		178			
B (1.0mg/cm^2 x 10cm^2)	12.8	83.8		1653		1732	
C (1.5mg/cm^2 x 10cm^2)	13.4	121.5	1.45	3080	1.86	3143	1.82
R(-)-N-desmethylselegiline							
A (0.5mg/cm^2 x 10cm^2)							
B (1.0mg/cm^2 x 10cm^2)	10.8	44.8		1067		1142	
C (1.5mg/cm^2 x 10cm^2)	10.6	65.6	1.46	1837	1.72	1879	1.65
R(-)-Methamphetamine							
A (0.5mg/cm^2 x 10cm^2)							
B (1.0mg/cm^2 x 10cm^2)	21.7	120.9		4734		5433	
C (1.5mg/cm^2 x 10cm^2)	17.3	188.1	1.56	7223	1.53	7779	1.43
R(-)-Amphetamine							
A (0.5mg/cm^2 x 10cm^2)							
B (1.0mg/cm^2 x 10cm^2)		42.6		1348		3405	
C (1.5mg/cm^2 x 10cm^2)	21.4	76.1	1.79	3264	2.4	3730*	*

actual applied doses (i.e, 5, 10 or 15 mg/10 cm2).

Study #5

Title: Dose Proportionality of Three Different Selegiline Transdermal System Formulations (0.5, 1.0 and 1.5 mg/cm^2 Selegiline) in Healthy Elderly Men and Women (Study# S9303-028-95B).

This was a randomized, single dose, three way crossover study to evaluate dose proportionality of three different STS dose formulations: 5 mg/10 cm^2, 10 mg/10 cm^2, 15 mg/10 cm^2. The patches were designed to release 1, 2 and 5 mg selegiline over 24 hour period. Twelve healthy male and twelve healthy female subjects between the ages of 54 to 76 years received a single dose of STS for 24 hours. Blood and urine samples were collected till 96 hours for determination of selegiline, desmethylselegiline, methamphetamine and amphetamine. Platelet MAO-B activity in each subject was determined till 24 hours.

The actual dose delivered from 5, 10 and 15 mg patch was 0.60, 2.24 and 4.17 mg/day. Both C_{max} and AUC increased disproportionally with increasing dose for selegiline and its all three metabolites.

Dose	Selegiline	Desmethylselegiline	Methamphetamine	Amphetamine
Cmax				
5	**66 ± 36**	**23 ± 9**	**91 ± 35**	**NM**
10	**243 ± 188**	**73 ± 72**	**246 ± 218**	**128 ± 81**
15	**741 ± 624**	**310 ± 392**	**842 ± 625**	**313 ± 212**
AUC (0-inf)				
5	**1710 ± 769**	**279 ± 219***	**10218 ± 5544**	**NM**
10	**6487 ± 4697**	**3324 ± 2634**	**20792 ± 11669**	**16824 ± 1928**
15	**21326 ± 18220**	**12314 ± 15745**	**48751 ± 42857**	**22751±18597**

The units of Cmax and AUC are pcg/mL and pcg*hr/mL

*AUC (0-t)

NM = No measurable plasma concentration.

Statistically, though no gender difference was noted in the pharmacokinetics of selegiline and its metabolites, the AUC and Cmax were lower in females than males and the difference widened with the increasing dose of selegiline. At 15 mg dose, the AUC

and Cmax in females were 43% and 38%, respectively. The following Table summarizes the pharmacokinetic parameters of selegiline and its metabolites in males and females.

Table 1. Mean (%CV) Pharmacokinetic Parameters

Treatment	AUCinf (pg*h/mL)		Cmax (pg/mL)		Ctrough (pg/mL)		half-life (h)	
	Male	Female	Male	Female	Male	Female	Male	Female
Selegiline								
A	2076.0 (38.0) n=3	1161.5 (29.4) n=2	63.3 (62.4) n=9	69.6 (49.9) n=9	49.6 (74.9) n=9	51.4 (59.4) n=9	13.37 (83.5) n=3	9.70 (77.3) n=2
B	7639.3 (68.2) n=8	4950.7 (76.6) n=6	275.6 (77.6) n=11	211.2 (76.2) n=11	230.0 (84.2) n=11	136.3 (79.4) n=11	14.91 (72.9) n=8	9.18 (47.8) n=6
C	28392.4 (83.4) n=9	14965.8 (56.1) n=10	914.5 (87.1) n=11	567.8 (59.9) n=11	820.0 (98.9) n=11	469.6 (52.7) n=10	19.11 (25.3) n=9	23.67 (32.4) n=10
Desmethylselegiline								
A	- (-)	- (-)	24.5 (46.0) n=4	22.0 (34.8) n=5	23.3 (53.4) n=4	18.8 (66.8) n=5	- (-)	- (-)
B	3768.3 (82.5) n=7	2545.3 (62.3) n=4	94.6 (97.6) n=11	50.1 (57.9) n=10	90.5 (102.7) n=11	43.7 (64.2) n=10	15.87 (34.8) n=7	20.55 (90.4) n=4
C	18636.1 (117.2) n=9	7132.7 (68.5) n=11	429.5 (121.4) n=11	189.6 (71.5) n=11	420.5 (124.1) n=11	178.4 (57.0) n=10	19.86 (35.6) n=9	29.73 (34.9) n=11
Methamphetamine								
A	8093.0 (81.7) n=2	12343.0 (44.7) n=2	81.8 (22.7) n=5	96.7 (45.6) n=7	73.2 (24.1) n=5	82.9 (63.8) n=6	55.05 (65.9) n=2	46.75 (26.8) n=2
B	22805.8 (65.3) n=6	18374.2 (38.3) n=5	282.1 (99.8) n=11	206.7 (57.7) n=10	246.6 (100.1) n=11	180.1 (58.4) n=9	35.10 (52.1) n=6	40.46 (32.7) n=5
C	62317.6 (94.1) n=9	36540.7 (44.7) n=10	929.1 (86.2) n=11	754.6 (53.3) n=11	821.0 (89.4) n=11	655.6 (53.4) n=10	30.80 (23.1) n=9	35.73 (31.9) n=10
Amphetamine								
A	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
B	16824.0 (11.5) n=2	- (-)	146.4 (73.5) n=7	106.2 (25.6) n=6	146.0 (68.0) n=5	74.0 (32.8) n=6	30.25 (5.4) n=2	- (-)
C	26946.8 (84.5) n=9	16456.5 (46.8) n=6	353.7 (73.9) n=10	276.0 (57.2) n=11	310.0 (64.6) n=9	234.0 (47.4) n=9	42.42 (45.0) n=9	37.48 (20.6) n=6

Due to small sample size it is difficult to make any conclusion about the gender difference in the pharmacokinetics of selegiline and its metabolites.

The platelet MAO-B activity decreased with dose. The mean percent inhibition of MAO-B activity in 24 hours for 5, 10 and 15 mg STS was 70 ± 22, 97 ± 3 and 100 ± 0.2, respectively. Based on maximum inhibition (Imax), the females have higher inhibition of MAO-B activity than males at 10 and 15 mg selegiline dose, whereas at 5 mg dose, the inhibition of MAO-B activity was higher in males than females. The difference was statistically significant but this difference may not be of any clinical significance. Therefore, like pharmacokinetics, it is also difficult to conclude if there is a gender difference in the inhibition of platelet MAO-B activity.

Treatment	Imax (pmol/10^8 platets/4 minutes)	
	Female	Male
STS (5.0mg/10cm^2)	256.8	361.3
STS (10.0mg/10cm^2)	484.8	419.5
STS (15.0mg/10cm^2)	289.4	227.0
Ratio 10mg STS/5mg STS (p-value)	1.89 (0.0228)	1.16 (0.6030)
Ratio 15mg STS/5mg STS (p-value)	1.13 (0.6770)	0.63 (0.0902)
Ratio 15mg STS/10mg STS (p-value)	0.60 (0.0777)	0.54 (0.0374)

Overall, the results of this study indicates that the pharmacokinetics of STS is non-linear over the dose range of 5 to 15 mg. Though statistically there is no gender difference in the pharmacokinetics of selegiline but the females appear to have lower levels of selegiline and its metabolites than the males. The MAO-B activity is dose and time dependent; by 24 hours the MAO-B inhibition was almost 100% at the selegiline doses of 10 and 15 mg. Small sample size is a hindrance in making any conclusion about the gender difference in the pharmacokinetics and pharmacodynamics of selegiline.

Study #5A

Title: Pharmacokinetic and pharmacodynamic evaluation of seven day administration of four different selegiline transdermal system (STS) formulations (0.5, 1.0 , and 1.5 mg/cm^2 (10 cm^2) and 1.5 mg/cm^2 (15 cm^2) selegiline in healthy elderly men and women (study # S9303-029-95B).

This was an open-label, randomized, multiple-dose, parallel design study in 48 healthy elderly (55-77 years of age) male (n =24) and female (n =24) volunteers. The subjects received four STS formulations (6 per group per gender): A: 0.5mg/cm^2, B: 1 mg/cm^2, C: 1.5 mg/cm^2 and D: 1.5 mg/cm^2, every 24 hours for 7 days. Patches A, B, and C were 10 cm^2 whereas patch D was 15 cm^2. The patch was applied on the upper torso and removed after 24 hours. The subjects were maintained on tyramine-free diet. Blood and urine samples for the determination of selegiline and its metabolites were collected at regular intervals till 264 and 192 hours, respectively. Blood samples for platelet MAO-B activity were taken at days -3, -2, -1 and 0 (prior to drug administration), 4, 12, 24, 192, 264, 360, 432, and 528 hours after the STS administration. Urine samples were also collected to determine MHPG sulfate, MHPG glucuronide and MHPG total (for MAO-A activity) till 192 hours.

The amount of drug delivered from patches A, B, C, and D was 0.68, 2.10, 4.39, and 5.69 mg, respectively. Plasma concentrations of selegiline and its metabolites increased with increasing dose, though not proportionally. Selegiline and its metabolite concentrations accumulated during multiple dosing until steady state was reached. Time to reach steady state for selegiline and its metabolites was dose dependent. It took 6 days for 0.5 mg/cm^2 patch (treatment A) to reach steady state whereas it took 5, 4, and 3 days for treatmants B, C, and D, respectively to reach steady state. The half-life of selegiline was 37, 38, 43 and 47 hours for formulations A, B, C and D, respectively. Less than 1% selegiline and desmethylselegiline were excreted unchanged in urine. The following Table summarizes the pharmacokinetic parameters of selegiline and its metabolites following different STS doses.

Table 5. Mean (%CV) Pharmacokinetic Parameters

Treatment	AUCinf (ng*h/mL)	Cmax (pg/mL)	Tmax (h)	Half-life (h)
Selegiline				
A	13.9 (92.9)	137 (81.6)	166.3 (4.8)	37.0 (60.2)
B	107.7 (36.8)	892 (34.1)	161.5 (6.9)	37.8 (27.8)
C	275.5 (36.1)	1992 (37.3)	144.0 (14.2)	43.0 (19.3)
D	463.9 (34.6)	3340 (39.6)	148.3 (21.8)	46.5 (29.7)
Desmethylselegiline				
A	6.4 (171.0)	86 (113.6)	166.0 (7.1)	-
B	80.2 (34.2)	660 (36.3)	160.7 (10.7)	34.8 (32.6)
C	174.2 (57.3)	1272 (55.0)	154.4 (14.2)	36.1 (18.1)
D	280.3 (49.0)	2308 (64.1)	156.5 (15.5)	39.1 (28.7)
Amphetamine				
A	12.1 (200.0)	123 (88.7)	147.3 (40.5)	-
B	113.0 (28.1)	831 (24.8)	168.0 (9.7)	45.9 (35.1)
C	307.1 (36.4)	2154 (38.3)	163.8 (12.7)	40.3 (26.6)
D	486.7 (38.4)	3587 (43.9)	164.5 (13.3)	35.9 (36.0)
Methamphetamine				
A	53.1 (62.7)	423 (43.8)	169.6 (0.8)	44.2 (15.0)
B	290.0 (37.7)	2118 (37.7)	161.4 (11.0)	41.3 (39.6)
C	673.3 (26.0)	4852 (32.5)	157.9 (13.0)	38.0 (18.7)
D	1027.4 (30.1)	7706 (38.0)	159.2 (14.0)	34.4 (31.9)

Table 6. Mean (%CV) Urinary Recovery

Treatment	*Selegiline*	*Desmethylselegiline*	*Amphetamine*	*Methamphetamine*
A	0.20 (151.5)	0.20 (128.8)	3.34 (106.3)	7.74 (73.5)
B	0.37 (65.5)	0.58 (37.4)	8.11 (24.5)	19.53 (26.6)
C	0.51 (62.7)	0.58 (32.9)	8.47 (24.5)	18.9 (17.0)
D	0.41 (56.1)	0.54 (45.3)	7.71 (36.4)	15.2 (34.1)

The platelet MAO-B activity started to decline within few hours (>10% inhibition by 4 hours) of the application of the patch. By 24 hours, the percent inhibition of platelet MAO-B activity was 62, 93, 99, and 100 following treatment A, B, C, and D, respectively. The MAO-B activity did not return to the baseline values till day 22 (528 hours) for all treatments. It should however, be noted that the inhibition and recovery of platelet MAO-B activity was dose dependent; at the lowest dose (treatment A), the inhibition was the least and the recovery was faster as compared to other three treatments.

The following Table summarizes the platelet MAO-B activities at different times for four formulations.

Table 8. LSM by treatment and time

	Treatment			
Time (h)	A	B	C	D
4	-12.1	-15.2	-38.3	-37.7
12	-28.0	-55.2	-88.7	-96.7
24	-61.2	-93.4	-99.6	-100.5
192	-99.3	-100.2	-100.2	-100.8
264	-94.7	-100.0	-100.3	-99.9
360	-73.3	-93.6	-98.9	-98.0
432	-49.8	-81.6	-94.4	-93.6
528	-17.6	-56.5	-76.5	-78.3
p-value testing LSM=0 at 528 hours	0.0004	0.0001	0.0001	0.0001

From the urinary recovery of MHPG following treatments A and C, it appears that there is some inhibition of MAO-A activity over 192 hours. The mean percent inhibition of MAO-A activity was 22% and 32%, respectively, following treatments A (0.5 mg) and C (1.5 mg). The results of treatments B and D were not presented by the Sponsor.

Conclusion:

The Cmax and AUC of selegiline increased with increasing dose in a non-linear fashion. The inhibition and the time to recovery of platelet MAO-B activity was dose dependent. At 1.5 mg/cm2 selegiline dose, only 30% inhibition of MAO-A activity was observed whereas at the same dose almost complete inhibition of MAO-B activity was noted.

Study #6

Title: Pharmacokinetie Evaluation of Multiple Dose (10-Day) Administration of Three Different Selegiline Transdermal System (STS) Formulations in Healthy Elderly Men (Study #S9303-031-95B).

This was a randomized, multiple-dose, parallel study in 18 healthy elderly male (65-78 years of age) volunteers. The subjects received three STS formulations, A: 20 mg/20 cm^2, B: 30 mg/20 cm^2, and C: 7.5 mg/5 cm^2, every 24 hours for 10 days in a parallel design. The patch was applied on the upper torso. The subjects were maintained on tyramine-free diet. Blood samples (7 mL) were collected at regular intervals till 360 hours. Urine samples were also collected till 360 hours. All 18 subjects completed the study.

Time to reach steady state for selegiline and its metabolites widely varied (120 to 168 hours). Plasma concentrations of selegiline and its metabolites increased with increasing dose, though not proportionally. The concentrations of selegiline and its metabolites were much lower with formulation C (7.5 mg/5 cm^2) than formulation B (30 mg/20 cm^2). Following 10 days of multiple dosing, accumulation of selegiline and its metabolites in plasma as compared to a single dose was observed. Following multiple dosing, two to three fold increase in the AUC of selegiline for formulations A and B and 5 fold increase for formulation C was noted. The accumulation of metabolites following multiple dosing was even higher than selegiline as compared to a single dose. The half-life of selegiline was 43, 52 and 42 hours for formulations A, B and C respectively. Less than 1% unchanged selegiline was found in urine. The following table summarizes the accumulation ratio (AUC following the 10th dose/AUC after single dose) of selegiline and its metabolites.

Dose	Selegiline	Desmethylselegiline	Methamphetamine	Amphetamine
A	3.48	7.58	33.17	16.95
B	2.04	4.93	19.86	11.75
C	5.05	101.10	-	46.00

Methamphetamine could not be detected after the first dose.

The following table summarizes the pharmacokinetic parameters of selegiline and its metabolites after single and multiple dosing of selegilne.

Table 1 Time to Peak Drug Concentration (hr) After the First and Last Application of Three Different Selegiline Transdermal System (STS) Formulations

	First Dose: STS Formulation			Last Dose: STS Formulation		
Drug	A	B	C	A	B	C
Selegiline	16.0	20.7	13.0	241	241	240
R(-)-N-Desmethylselegiline	22.7	24.0	24.0	242	241	241
R(-)-Amphetamine	20.7	22.0	24.0	245	244	246
R(-)-Methamphetamine	24.0	24.0	24.0	243	243	242

Data presented as the mean
STS-A: 20.0mg/20cm^2; STS-B: 30.0mg/20cm^2; STS-C: 7.5mg/5cm^2

Table 2 Maximal Plasma Drug Concentration (pg/mL) After the First and Last Application for Three Different Selegiline Transdermal System (STS) Formulations

	First Dose: STS Formulation			Last Dose: STS Formulation		
Drug	A	B	C	A	B	C
Selegiline	665 (33)	1954 (42)	184 (47)	2361 (26)	3723 (16)	750 (15)
R(-)-N-Desmethylselegiline	286 (38)	827 (28)	17 (155)	1346 (31)	2814 (30)	402 (49)
R(-)-Amphetamine	234 (35)	665 (37)	-	2056 (31)	5461 (33)	884 (35)
R(-)-Methamphetamine	589 (38)	1940 (37)	124 (79)	3974 (26)	11615 (25)	1968 (28)

Data presented as the mean (%CV)
STS-A: 20.0mg/20cm^2; STS-B: 30.0mg/20cm^2; STS-C: 7.5mg/5cm^2

Table 3 Area Under the Plasma Drug Concentration Time Curve (pg•hr/mL) After the First and Last Application for Three Different Selegiline Transdermal System (STS) Formulations

	First Dose: STS Formulation			Last Dose: STS Formulation		
Drug	A	B	C	A	B	C
Selegiline	9520 (38)	26714 (44)	2109 (39)	33107 (25)	54426 (25)	10654 (20)
R(-)-N-Desmethylselegiline	2930 (58)	9758 (33)	67 (155)	22217 (36)	48116 (35)	6774 (54)
R(-)-Amphetamine	1280 (52)	5595 (52)	-	42460 (36)	111135 (36)	17850 (36)
R(-)-Methamphetamine	4604 (44)	19533 (52)	832 (101)	78018 (28)	229432 (30)	38268 (32)

Data presented as the mean (%CV)
STS-A: 20.0mg/20cm^2; STS-B: 30.0mg/20cm^2; STS-C: 7.5mg/5cm^2

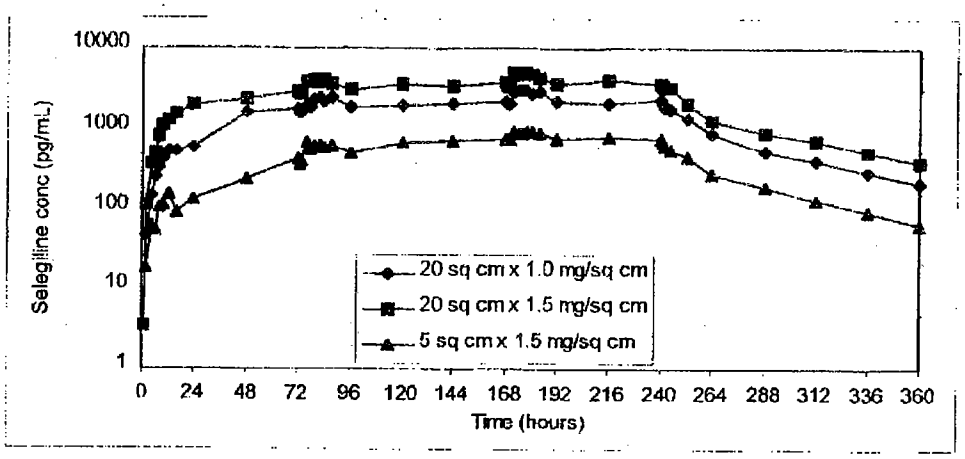


Figure 14. **Mean Selegiline Concentration-Time Profiles in Healthy Elderly Males after 10-Day Administration of Three Selegiline Transdermal Formulations**

Study #7

Title: Steady state pharmacokinetic comparison of the 10 mg and 20 mg selegiline transdermalsystem in healthy male volunteers (S9303-P9923).

In this multiple dose study, 12 healthy male subjects (21-40 years of age) received two STS formulations: 10 mg/20 cm^2 or 20 mg/20 cm^2 every 24 hours for 10 days in a cross-over design. The patch was applied on the upper torso. Blood samples (7 mL) were collected according to following schedule:

Study Period 1		Study Period 2	Collection Times
Day 1	and	Day 15	0800[a] (30 minutes prior to dosing), blank 0h plasma
Day 7	and	Day 21	0800, trough plasma
Day 8	and	Day 22	0800, trough plasma
Day 9	and	Day 23	0800, trough plasma
Day 10	and	Day 24	0800 (0h pre-dose) and 1, 2, 4, 6, 8, 10, 12, 14, 18 hours post-dose
Day 11	and	Day 25	0800 24, 24.5, 26, 28, 30, 36h post-dose
Day 12	and	Day 26	0800 (48h post-dose)
Day 13	and	Day 27	0800 (72h post-dose)
Day 14	and	Day 28	0800 (96h post-dose)

[a]24h clock

Eleven subjects completed the study. The actual dose delivered from 10 and 20 mg patch was 1.5 and 4.6 mg/day. The AUC(0-24) values indicate that selegiline was not dose proportional. The AUC(0-24) was approximately 3.6 times higher for 20 mg patch as compared to 10 mg patch. The C_{max} and C_{min} of selegiline followed the same pattern as of AUC(0-24). The half-life of selegiline for 20 mg patch was slightly longer (30 hours) than the 10 mg patch (21 hours).

The following table summarizes the pharmacokinetic parameters of selegiline and its metabolites.

Mean (%CV) Pharmacokinetic Parameters for the STS 10 mg/20 cm² (N=11)

Pharmacokinetic Parameter	Selegiline	N-desmethylselegiline	L-methamphetamine	L-amphetamine
	Mean (%CV)	Mean (%CV)	Mean (%CV)	Mean (%CV)
$AUC_{(0-24)}$ [pg*hr/mL]	16533 (19)	10714 (27)	36380 (30)	15871 (22)
$AUC_{(0-24)}$ M/P	N/A	0.65 (21)	2.25 (32)	0.98 (23)
CL [L/hr]	628.58 (22)	N/A	N/A	N/A
CL_r [L/hr]	0.3418 (55)	0.6692 (33)	7.8863 (25)	7.3021 (25)
C_{max} [pg/mL]	827.0 (20)	550.5 (30)	1844.6 (34)	840.7 (27)
C_{min} [pg/mL]	497.5 (21)	349.8 (29)	1168.5 (30)	476.2 (28)
C_{ss} [pg/mL]	688.9 (19)	446.4 (27)	1516.1 (30)	661.4 (22)
%Fe	0.0560 (61)	0.5011 (42)	22.4322 (32)	10.1343 (28)
Fluctuation %	68.97 (48)	58.03 (39)	57.78 (39)	78.82 (30)
$T_{½}$ [hr]	21.58 (37)	18.25 (37)	22.79 (22)	23.16 (37)
K_{el} [1/hr]	0.0372 (44)	0.0449 (48)	0.0315 (17)	0.0330 (29)
MRT [hr][a]	12.32 (3)	12.14 (2)	12.31 (4)	12.36 (4)
T_{max} [hr]	11.63 (52)	12.54 (28)	14.18 (32)	16.00 (29)
Apparent Dose [mg]	1.51 (39)	N/A	N/A	N/A

[a]MRT for metabolites are uncorrected values (uncorrected for parent selegiline).

Mean (%CV) Pharmacokinetic Parameters for the STS 20 mg/20 cm² (N=11)

Pharmacokinetic Parameter	Selegiline	N-desmethylselegiline	L-methamphetamine	L-amphetamine
	Mean (%CV)	Mean (%CV)	Mean (%CV)	Mean (%CV)
$AUC_{(0-24)}$ [pg*hr/mL]	58978 (18)	35883 (20)	133980 (27)	60952 (21)
$AUC_{(0-24)}$ M/P	N/A	0.62 (22)	2.31 (29)	1.05 (23)
CL [L/hr]	349.59 (18)	N/A	N/A	N/A
CL_r [L/hr]	0.3821 (63)	0.8570 (22)	9.1650 (37)	8.5362 (37)
C_{max} [pg/mL]	3019.4 (23)	1794.8 (20)	6470.1 (30)	3010.9 (25)
C_{min} [pg/mL]	1949.9 (18)	1207.3 (22)	4537.3 (25)	2000.1 (23)
C_{ss} [pg/mL]	2457.41 (18)	1495.1 (20)	5582.5 (27)	2539.7 (21)
%Fe	0.1097 (57)	0.7439 (30)	32.0655 (22)	15.3150 (28)
Fluctuation %	54.06 (29)	49.69 (28)	41.81 (39)	51.48 (44)
$T_{½}$ [hr]	30.54 (43)	25.62 (33)	25.00 (27)	25.07 (28)
K_{el} (1/hr)	0.0258 (32)	0.0321 (59)	0.0291 (20)	0.0290 (20)
MRT [hr][a]	12.09 (3)	11.92 (3)	12.16 (3)	12.29 (3)
T_{max} [hr]	11.73 (54)	11.64 (37)	12.55 (44)	12.00 (43)
Apparent Dose (mg)	4.55 (26)	N/A	N/A	N/A

[a]MRT for metabolites are uncorrected values (uncorrected for parent selegiline).

Study #8

Title: Single dose pharmacokinetic study of transdermal selegiline 20 mg patches in renally compromised patient (Study # 9303-9811).

The effect of renal dysfunction on the pharmacokinetics of selegiline was studied in three groups of patients (4 per group) with various degrees of renal dysfunction. There were six males and six females in the study. The age of the patients ranged from 46 to 80 years. The creatinine clearance in 3 different groups were as follows: Mild group = 50-80 mL/min/1.73 m^2, moderate group = 30-49 mL/min /1.73 m^2, and severe group = <30 mL/min/1.73 m^2. Each patient received a single dose of 20mg/20 cm^2 STS for 24 hours. The average dose of selegiline delivered from the STS was 4.01 mg (2.05-5.56 mg). Blood samples were collected till 120 hours. The results of the study indicated that compared to a historical control group (healthy subjects), the AUC and Cmax of selegiline in patients with renal impairment were comparatively lower by 30% to 45%. Due to small sample size and high variability in the pharmacokinetics of selegiline it is however, difficult to assess if indeed compared to a historical control group, the AUC and Cmax of selegiline in patients with renal impairment are lower. The AUC and Cmax values were almost similar among patients with mild, moderate and severe renal impairment. This is not surprising as selegiline is extensively metabolized and less than 1% unchanged drug is excreted in urine in healthy subjects.

The pharmacokinetic parameters of selegiline STS (20 mg/20 cm^2) in patients with renal impairment and 10 healthy subjects (from a previous study) has been summarized in the following Table. The dose delivered from the patch in healthy subjects was 4.78 mg (study S9303-P9809 of the Sponsor and study #1 in this review).

Pharmacokinetic parameters of selegiline in patients with renal impairment

Parameters	Mild	Moderate	Severe	Healthy subjects
AUCinf	27945 (18)	24660 (56)	30180 (27)	46162 (61)
Cmax	1129 (21)	1079 (48)	1550 (24)	2162 (78)
$T_{1/2}$ (hrs)	57 (75)	26 (89)	21 (84)	20 (44)

The units of Cmax and AUC are pcg/mL and pcg*hr/mL
Numbers in parentheses are %CV.

Pharmacokinetic parameters of desmethylselegiline in patients with renal impairment

Parameters	Mild	Moderate	Severe	Healthy subjects
AUCinf	7634 (51)	9660 (57)	14486 (43)	22960 (68)
Cmax	286 (49)	352 (41)	428 (53)	791 (67)
$T_{1/2}$ (hrs)	17 (36)	16 (39)	18 (85)	15 (52)

The units of Cmax and AUC are pcg/mL and pcg*hr/mL
Numbers in parentheses are %CV.

Pharmacokinetic parameters of amphetamine in patients with renal impairment

Parameters	Mild	Moderate	Severe	Healthy subjects
AUCinf	30999 (26)	50811 (33)	58690 (22)	42692 (50)
Cmax	404 (42)	428 (47)	730 (35)	796 (56)
$T_{1/2}$ (hrs)	53 (55)	64 (60)	40 (42)	25 (22)

The units of Cmax and AUC are pcg/mL and pcg*hr/mL
Numbers in parentheses are %CV.

Pharmacokinetic parameters of methamphetamine in patients with renal impairment

Parameters	Mild	Moderate	Severe	Healthy subjects
AUCinf	53530 (53)	75379 (33)	105637 (17)	93088 (59)
Cmax	988 (69)	1025 (50)	1657 (39)	2171 (52)
$T_{1/2}$ (hrs)	41 (37)	52 (49)	35 (38)	21 (23)

The units of Cmax and AUC are pcg/mL and pcg*hr/mL
Numbers in parentheses are %CV.

Conclusion:

Since less than 1% selegiline is excreted in urine and it also appears that the pharmacokinetics of selegiline among patients with different degrees of renal impairment (mild, moderate and severe) are not different, no dosage adjustment of selegiline is required in patients with renal impairment.

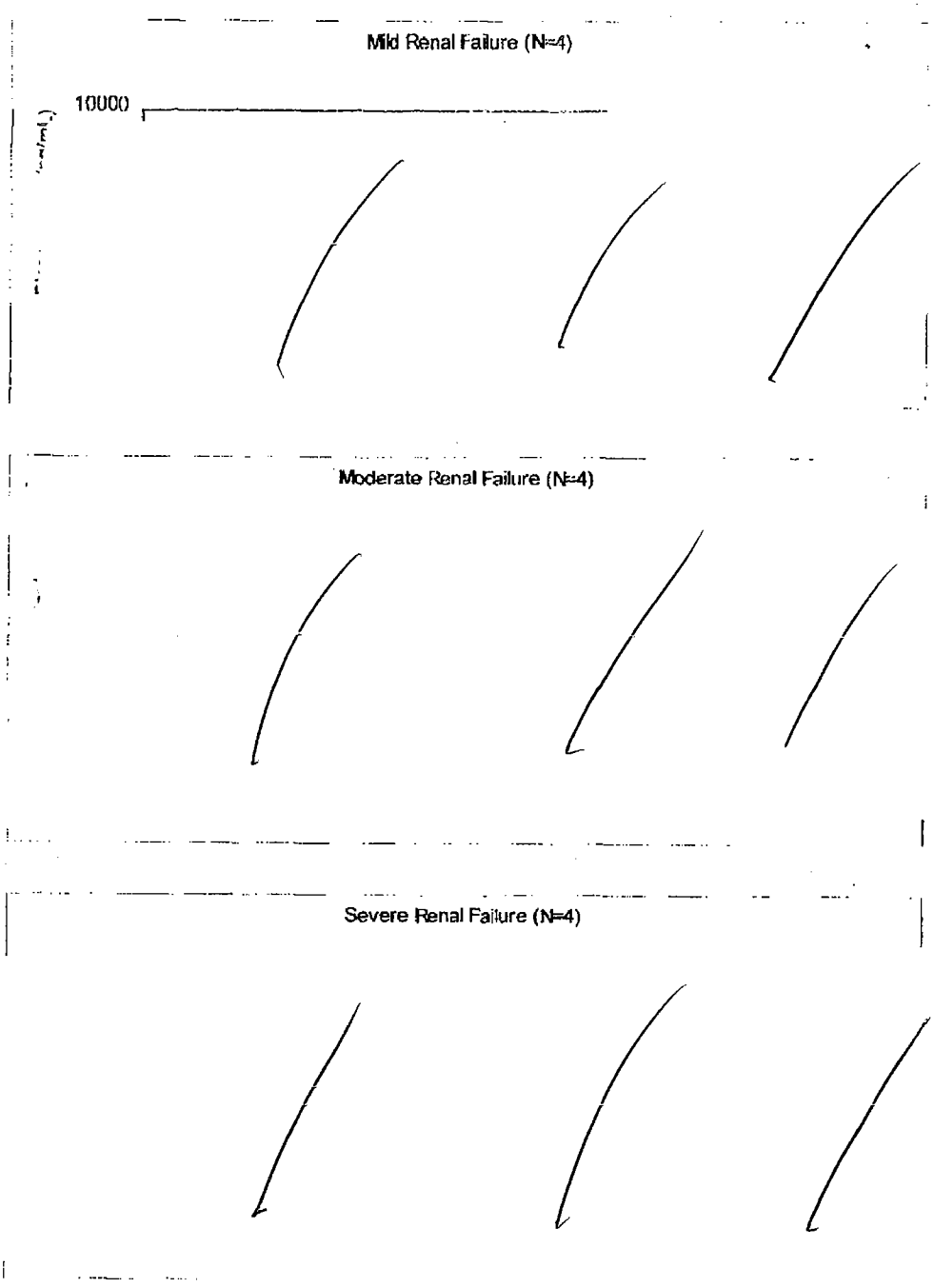


Figure 16. **Plasma Concentration-Time Profiles of Selegiline and its Metabolites in Patients with Varying Degrees of Renal Impairment after Single Application of STS (20 mg/20 cm^2)**

Study #9

Title: Single dose pharmacokinetic study of transdermal selegiline 20 mg patches in hepatic disease patient (Study # 9303-9812).

The effect of hepatic impairment on the pharmacokinetics of selegiline was studied in eight patients (six male and two female) with hepatic impairment. The age of the patients ranged from 41 to 54 years. There were seven patients with Child-Pugh of class B (moderate hepatic impairment) and 1 with class A (mild hepatic impairment). Each patient received a single dose of 20mg/20 cm^2 STS for 24 hours. The average apparent dose of selegiline delivered from the STS was 3.96 mg. Blood samples were collected till 96 hours. The results of the study indicated that compared to a historical control group (healthy subjects), the AUC and Cmax of selegiline in patients with hepatic impairment were one-third of the healthy subjects. The metabolite to parent ratio (based on AUCinf) in patients with hepatic impairment for desmethylselegiline, amphetamine and methamphetamine was 0.57, 1.35 and 6.36, respectively. In healthy subjects, this ratio was 0.57, 0.9 and 2.0, respectively. The half-lives of selegiline, desmethylselegiline in patients with hepatic impairment were comparable with healthy subjects but the half-lives of methamphetamine and amphetamine in patients with hepatic impairment were 5 and 2-fold longer as compared to healthy subjects. Due to small sample size it is difficult to conclude if indeed hepatic impairment (mild or moderate) alters the pharmacokinetics of selegiline and its metabolites compared to healthy subjects. The pharmacokinetic parameters in patients with hepatic impairment have been summarized in the Table (overleaf).

The pharmacokinetic parameters of selegiline STS (20 mg/20 cm^2) in 10 healthy subjects (from a previous study) has been summarized in the following Table. The dose delivered from the patch was 4.78 mg (study S9303-P9809 of the Sponsor and study #1 in this review).

Dose	Selegiline	Desmethylselegiline	Methamphetamine	Amphetamine
AUCinf	46162 (61)	22960 (68)	93088 (59)	42692 (50)
Cmax	2162 (78)	791 (67)	2171 (52)	796 (56)
$T_{1/2}$ (hrs)	20 (44)	15 (52)	21 (23)	25 (22)

The units of Cmax and AUC are pcg/mL and pcg*hr/mL
Numbers in parentheses are %CV.

Pharmacokinetic Parameter[a]	Selegiline	N-desmethylselegiline	L-amphetamine	L-methamphetamine[b]
AUCI, pg*hr/mL	15753 (60.1)	8825 (35.9)[c]	29213 (25.8)[d]	68731 (69.2) [55822 (59.0)][e]
$AUC_{(0-24)}$, pg*hr/mL	9698 (66.5)	3115 (61.7)[c]	2015 (74.7)	7638 (53.6) [8450 (43.3)]
AUCI M/P Ratio	--	0.57 (60.3)	1.35 (32.9)[d]	6.36 (117.0) [3.82 (53.4)]
AUCT, pg*hr/mL	14835 (62.0)	5883 (63.9)	11509 (80.7)	38996 (46.8) [42048 (41.3)]
AUCT M/P Ratio	--	0.40 (51.1)	0.71 (82.4)	3.06 (39.8) [3.10 (42.4)]
CL, L/hr[f]	329 (51.1)	--	--	--
CL_T, L/hr	1.71 (83.0)	1.58 (74.0)[c]	2.90 (53.1)[d]	4.01 (52.8) [4.52 (36.8)]
C_{max}, pg/mL	742 (61.8)	288 (56.6)	343 (52.1)	939 (47.9) [1024 (40.2)]
%Fe	0.7504 (121)	0.2929 (85.0)[g]	2.9718 (82.4)[g]	7.1509 (80.3)[g] [7.8334 (74.6)][g]
$T_{½}$, hr	17.72 (56.5)	15.66 (62.3)[c]	49.20 (60.6)[d]	93.02 (174) [36.03 (42.2)]
K_{el}, 1/hr	0.0539 (58.7)	0.0595 (53.8)[c]	0.0172 (44.9)[d]	0.0194 (52.7) [0.0220 (36.2)]
MRT, hr[h]	29.2 (29.2)	35.6 (48.5)[c]	87.7 (45.9)[d]	149.6 (156) [72.0 (33.0)]
T_{lag}, hr	1.25 (37.0)	7.75 (50.6)	16.5 (44.8)	8.50 (51.5) [7.71 (52.8)]
T_{max}, hr	21.8 (17.0)	24.3 (1.1)	28.5 (7.3)	26.9 (10.0) [26.43 (9.7)]

[a]N=8 except where noted

[b]*Pharmacokinetic parameters for L-methamphetamine were calculated with and without [bracketed] Patient 06 data.*

[c]n=6; [d]n=3; [e]n=7 (excluding data from Patient 06 [bracketed values])

[f]Apparent plasma clearance of the metabolites could not be calculated, as the metabolites were dosed separately.

[g]Ratio of metabolite/parent molecular weight was used in this calculation.

[h]MRT for metabolites are uncorrected values (uncorrected for parent *selegiline*).

AUCT=area under the concentration-time curve; CL=total clearance; CL_T=renal clearance; C_{max}=maximum concentration over the entire sampling phase; %Fe=apparent fraction excreted; K_{el}=apparent elimination rate constant; M/P=metabolite/parent drug; MRT=mean residence time; T_{lag}=time interval from dosing to time of first measurable concentration; T_{max}=time to attain C_{max}

Note: Data expressed as mean (%CV); STS 20 mg (1.0 mg/cm^2) Lot # 26E007D

Note: R(-)-N-desmethylselegiline, R(-)-amphetamine, and R(-)-methamphetamine are interchangeable terms for N-desmethylselegiline, L-amphetamine, and L-methamphetamine, respectively.

Conclusion:

Since selegiline is extensively metabolized, it will be anticipated that hepatic impairment will increase selegiline levels and decrease the metabolite levels. In this study, selegiline and desmethylselegiline concentrations are almost one-third in the patients with hepatic impairment as compared to healthy subjects. The concentrations of amphetamine and methamphetamine, however, are almost two-third in the patients with hepatic impairment as compared to historical healthy subjects. From this study it is difficult to draw any conclusion about the impact of hepatic impairment on the pharmacokinetics of selegiline mainly due to small sample size used in this study. Based on the results of the study dosage adjustment of selegiline may not be required in patients

with hepatic impairment, however, caution should be employed in this patient population when selegiline is given.

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Study #11

Title: Effect of chronic transdermal selegiline 20 mg administration on the pharmacokinetics of racemic warfarin after steady-state administration in healthy volunteers (Study #S9303-P9919).

This was an open-label, two-phase, single center study in healthy male subjects (n = 8, 18-45 years of age). During the first phase of the study, the subjects were maintained on a stable warfarin therapy (days 1-10). Warfarin dose was titrated to achieve a targeted international normalized ratio (INR) of 1.5 to 2.0. After the titration, each subject remained on the same warfarin dose for the remainder of the study (days 11-21). During the second phase of the study, subjects received the STS (20 mg/20 cm^2) once daily for 7 days while remaining on their warfarin maintenance dose. Trough blood samples were collected from day 11 to day 21 for the measurment of warfarin (S and R) concentrations in plasma. Blood samples for the measurement of selegiline and its metabolite concentrations in plasma were collected from day 15 to day 22 (0, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 48, 72, 96, 120, 144 and 168 hours).

The results of the study indicated that STS did not alter the steady state plasma concentrations of warfarin (R and S). According to the Sponsor, the STS did not significantly alter factors VII and X (please see figure, page# 81). Furthermore, the Sponsor claims that a slight increase in the INR levels may not be of any clinical significance (please see figure, page# 81).

For medical reviewer: Please evaluate if indeed slight changes in factors VII and X as well as INR values are of no clinical significance.

Mean (%CV) Pharmacokinetic Parameters for Selegiline and Metabolites with Co-Administration of Warfarin (N=8, Completed Subjects)

Pharmacokinetic Parameters	Selegiline		R(-)-N-desmethylselegiline		R(-)-amphetamine		R(-)-methamphetamine	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
$AUC_{(0-24)}$[a] (pg*hr/mL)	19614.02	42.86	4643.93	54.36	3332.58	61.67	11706.84	62.36
$AUC_{(0-24)}$ M/P	-	-	0.22	36.31	0.15	32.10	0.56	24.86
CL[a](L/hr)	1275.27	60.32	-	-	-	-	-	-
C_{max}[a] (pg/mL)	1296.90	40.57	351.60	53.59	339.60	54.51	1047.80	64.60
MRT[a] (hr)	13.16	7.68	16.85	17.40	19.05	12.36	17.42	4.86
T_{max} (hr)	12.25	22.14	20.74	21.78	21.73	19.28	21.73	19.28

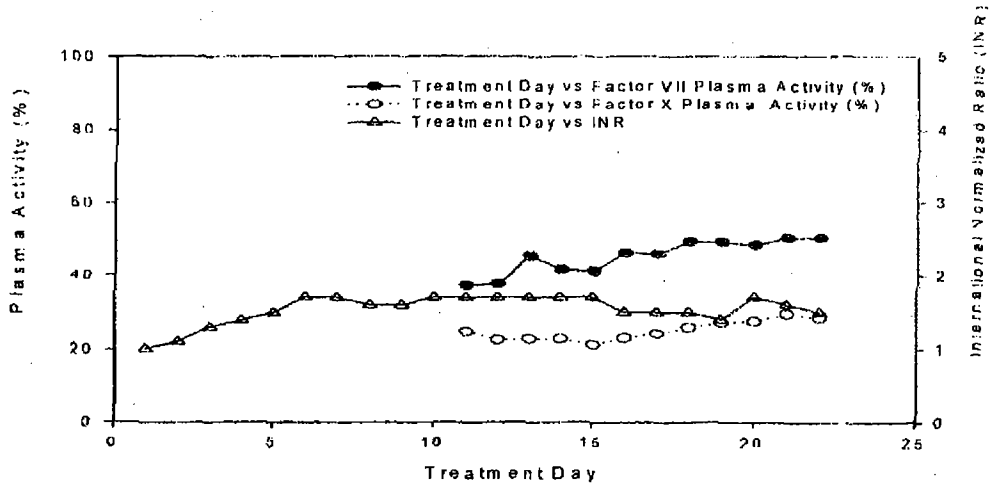
[a]Mean values for $AUC_{(0-24)}$, CL, MRT, and peak plasma concentrations (C_{max}) for selegiline and its metabolites were based on estimates for the first day of selegiline administration (Day 15 of the study).
$AUC_{(0-24)}$=area under the plasma concentration-time curve over a period of 24 hours after the 1st dose only; CL=total clearance; C_{max}=maximum concentration over the 24-hour dosing interval; CV=coefficient of variation; M/P=metabolite to parent; MRT=mean residence time; T_{max}=time to attain C_{max}
Note: R(-)-N-desmethylselegiline, R(-)-amphetamine and R(-)-methamphetamine are used interchangeably for N-desmethylselegiline, L-amphetamine, and L-methamphetamine, respectively.
Data Source: Appendix C.1

4. No evidence of an alteration in the pharmacokinetic behavior of the individual enantiomers of warfarin was observed (table below). Steady-state trough levels of both R and S warfarin were unchanged in the presence of the STS (20 mg/20 cm^2).

Time (Days)	R Warfarin		S Warfarin	
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV
11[a]	648.9	36.7	386.9	38.7
12[a]	672.6	39.3	398.3	42.2
13[a]	660.3	37.7	398.0	42.8
14[a]	674.5	52.5	400.9	47.4
15[b]	667.1	46.4	409.5	48.8
16[b]	673.1	40.4	406.0	48.2
17[b]	667.3	40.1	403.5	47.8
18[b]	672.1	41.5	409.8	51.7
19[b]	698.4	44.1	411.8	47.6
20[b]	664.3	45.4	407.0	44.8
21[b]	708.6	46.0	425.8	40.6
22[c]	634.8	41.5	386.6	45.8

[a]Individualized maintenance (stable) dose of warfarin on Days 11 through 14
[b]Individualized maintenance (stable) dose of warfarin continued during treatment with warfarin plus STS (20 mg/20 cm^2) on Days 15 through 21
[c]24 hr post-last-dose
CV=coefficient of variation; R and S=enantiomers of warfarin
Data Source: Appendix C.1

Mean INR Values, Factor VII, and Factor X % Plasma Activity Composite (N=8, Completed Subjects)



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Study #12

Title: Steady-state pharmacokinetic drug interaction study between alprazolam and selegiline transdermal system in healthy volunteers (Study #S9303-P9920).

This was an open-label, randomized, 3 period, 3-treatment, 6-way latin square crossover study in 12 subjects (10 males and 2 females, 21-44 years of age). Six groups of subjects (2 each group) were randomized to one of six treatment sequences of three treatments for 7 days each (3 weeks total):
Treatment A : STS 20 mg/20 cm^2 alone.
Treatment B : STS 20 mg/20 cm^2 + alprazolam
Treatment C : Alprazolam alone.

	Treatment Period[a]		
Subject Group[b]	1	2	3
Group I	STS	STS + Alprazolam	Alprazolam
Group II	STS + Alprazolam	Alprazolam	STS
Group III	Alprazolam	STS	STS + Alprazolam
Group IV	Alprazolam	STS + Alprazolam	STS
Group V	STS + Alprazolam	STS	Alprazolam
Group VI	STS	Alprazolam	STS + Alprazolam

[a]Each treatment period was 7 days in duration with no time interval between treatments.
[b]Two subjects per group.

Selegiline was administered once daily for 7 days for treatment A and B and 0.5 mg alprazolam tablets three times daily for seven days for treatments B and C. Blood samples (7 mL) were collected at the following schedule:

Table 3.3. Blood Sampling Schedule

Displayed for Treatment Sequence ABC								
Treatment A[a]			Treatment B[a,b]			Treatment C[a]		
Day	Hour	Time	Day	Hour	Time	Day	Hour	Time
1	0[b]	0800[c]	11[d]	0	0800	18[d]	0	0800
4	0[d]	0800	12[d]	0	0800	19[d]	0	0800
5	0[d]	0800	13[d]	0	0800	20[d]	0	0800
6	0[d]	0800	14[d]	0	0800	21[d]	0	0800
7	0[d]	0800		0.25	0815		0.25	0815
	0.5	0830		0.5	0830		0.5	0830
	1	0900		1	0900		1	0900
	2	1000		1.5	0930		1.5	0930
	4	1200		2	1000		2	1000
	6	1400		4	1200		3	1100
	8	1600		6	1400		4	1200
	10	1800		8	1600		6	1400
	12	2000		10	1800		8	1600
	14	2200		12	2000			
	18	0200		14	2200			
	24	0800		18	0200			
				24	0800			

[a]Treatment A: STS 20 mg/20 cm^2 monotherapy; Treatment B: STS 20 mg/20 cm^2+ alprazolam; Treatment C: alprazolam monotherapy.
[b]A minimum blood volume of 10 mL was collected on Day 1 (pre-dose) and during Treatment B to allow for split aliquots of 5 mL each for separate assay of selegiline and alprazolam. At all other sampling timepoints, a minimum blood volume of 7 mL was collected.
[c]30 minutes prior to dosing
[d]Blood sampling for trough concentrations

The results of the study indicated that alprazolam did not alter the steady state pharmacokinetics of the STS. Alprazolam decreased the AUC and Cmax of selegiline by 14% and 18%, respectively. In general in majority of the subjects the AUC and Cmax of selegiline was slightly lower when given with alprazolam as compared to selegiline alone. Selegiline metabolite levels were also slightly lower when given with alprazolam as compared to selegiline alone. Furthermore, STS produced no effect on the pharmacokinetics of alprozalam.