CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-336/21-708

PHARMACOLOGY REVIEW(S)

MEMORANDUM

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

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: 1/29/04

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 21-336

Issues raised in the Agency's Not Approvable letter (dated 3/25/02), related to pharmacology/toxicology, were: (1) the need for electronic datasets for the mouse and rat carcinogenicity studies in order to allow for an independent evaluation of the data, (2) a repeat Ames test using drug concentrations sufficient to achieve adequate cytotoxicity in each tester strain, with and without metabolic activation, (3) the need for the sponsor to address the adequacy of the *in vivo* cytogenetics assay conducted by [redacted] None of these issues was a basis for the NA action.

The sponsor's response to the Agency's NA letter was reviewed by Paul Roney, Ph.D. (Pharmacology/Toxicology Review and Evaluation, 1/28/04). Dr. Roney also addressed issues related to the sponsor's proposal to market higher dosage forms (30, 40 mg) than was studied in the original NDA (i.e., 20 mg). Dr. Roney concluded that the repeat *in vitro* Ames assay and the *in vivo* micronucleus assay conducted by the sponsor were adequate and that, therefore, "...the genotoxic potential of selegiline has been adequately examined". Regarding the carcinogenicity studies, Dr. Roney concluded that the 78-wk mouse study was inadequate (based on short duration, incomplete histopathology, and the lack of significant tumor findings) and recommended that the sponsor conduct Phase IV "either a two year or an alternative carcinogenicity study in mouse" and "a six month dermal study using an appropriate model, such as the minipig", the latter study designed to detect "the potential for selegiline to induce preneoplastic foci". Regarding the higher clinical doses, Dr. Roney concluded that plasma exposures obtained in the chronic and the reproductive toxicology studies were adequate to support the 30- and 40-mg human doses.

• Regarding the sponsor's assessment of genotoxic potential, one concern remains. The *in vivo* micronucleus assay was conducted in the mouse using oral dosing. In animals and human, circulating levels of selegiline relative to metabolites (i.e., the selegiline-to-metabolite ratios) are notably higher following transdermal as compared to oral dosing. The sponsor was asked to provide pharmacokinetic/toxicokinetic data in mouse (to support the use of the oral carcinogenicity study in mouse in the assessment of the carcinogenic potential of selegiline administered transdermally). No plasma exposure data were provided for the mouse. Therefore, there are insufficient data to determine whether or not there was adequate exposure to selegiline in the *in vivo* micronucleus assay. The sponsor should be asked to either justify the use of the

oral route in this assay or conduct a repeat *in vivo* micronucleus assay using a route that would result in higher circulating levels of selegiline.

• Regarding the sponsor's assessment of carcinogenic potential, the 78-wk mouse study is inadequate based on the short duration, the incomplete histopathology, and the insensitivity of the assay at the high dose. The high dose is problematic due to the marked decreases in body weight and body weight gain (relative to controls). Such effects on body weight have been thought to reduce sensitivity to spontaneous and drug-induced tumors (depending on the target organ). And, in the mouse study, there were decreases in overall tumors at the high dose, and no significant increases in any tumor type at any dose in either males or females. (The ExeCAC concurred with this assessment [meeting minutes appended to Dr. Roney's review].) As noted previously, the sponsor did not provide any pharmacokinetic/toxicokinetic data by which to estimate plasma exposure to selegiline or metabolites in the 78-wk study. Based on these considerations, it would seem prudent to

Problems with incomplete histopathology and excessive body weight effects at the high dose also apply to the 2-yr carcinogenicity study in rat. The lack of an examination of a complete battery of tissues is somewhat ameliorated by the fact that many of the tissues not examined in the 2-yr study were examined in the 6-month transdermal study in rat, and no apparent drug-related microscopic findings were detected. Regarding dose, the mid dose was associated with a small body weight effect (10-16% decrease in body wt relative to controls), and plasma data (from a 14-day bridging study) would suggest that exposure to the metabolites, N-desmethylselegiline, l-amphetamine, and l-methamphetamine, at the mid-dose in rat was fairly similar to that average expected in humans at the maximum recommended dose (MRHD) of 40 mg/day. However, plasma exposure to selegiline in rat at the mid-dose used in the 2-yr study appeared to be markedly lower (0.04-0.2 times) than the expected exposure at the MRHD. (In rat, exposure at the mid dose was estimated since only one dose level, the high dose in the 2-yr oral study, was tested. In humans, circulating levels of selegiline are 14 times higher following transdermal than following oral dosing at the approved dose (i.e., 5 mg b.i.d.) Dr. Roney has pointed out one other issue, i.e., neither the mouse or rat study assessed tumorigenic potential at the application site.

As noted by Dr. Roney, concern regarding the adequacy of the carcinogenicity assessment is heightened by the fact that selegiline was both mutagenic and clastogenic in an *in vitro* mouse lymphoma tk assay, both in the presence and absence of metabolic activation.

Therefore, as Dr. Roney recommended, the sponsor should further investigate the carcinogenic potential of seligiline. However, instead of separate studies to assess carcinogenic potential and preneoplastic changes at the application site, the sponsor could address both local and systemic tumorigenic effects by conducting a 2-yr dermal carcinogenicity study, preferably in mouse (since there are relevant data in the rat). An alternative animal model, e.g., the TG.AC mouse model, is generally considered an acceptable alternative to a 2-yr bioassay, particularly for dermal drug products. However, since neither the mouse nor the rat oral study adequately addressed the tumorigenic potential of selegiline itself, it is recommended that the sponsor conduct a 2-yr bioassay in mouse; this study may be completed Phase 4. This recommendation is predicated, in part, on the assumption that higher plasma exposure to selegiline can be obtained in the mouse with dermal application, and at doses that do not have excessive effects on body weight. As previously noted, no plasma exposure data are available in mouse. However, in a 6-month study

in rat, notably higher plasma levels of selegiline appear to have been achieved with transdermal than with oral dosing at the high dose used in the 2-yr oral carcinogenicity study.

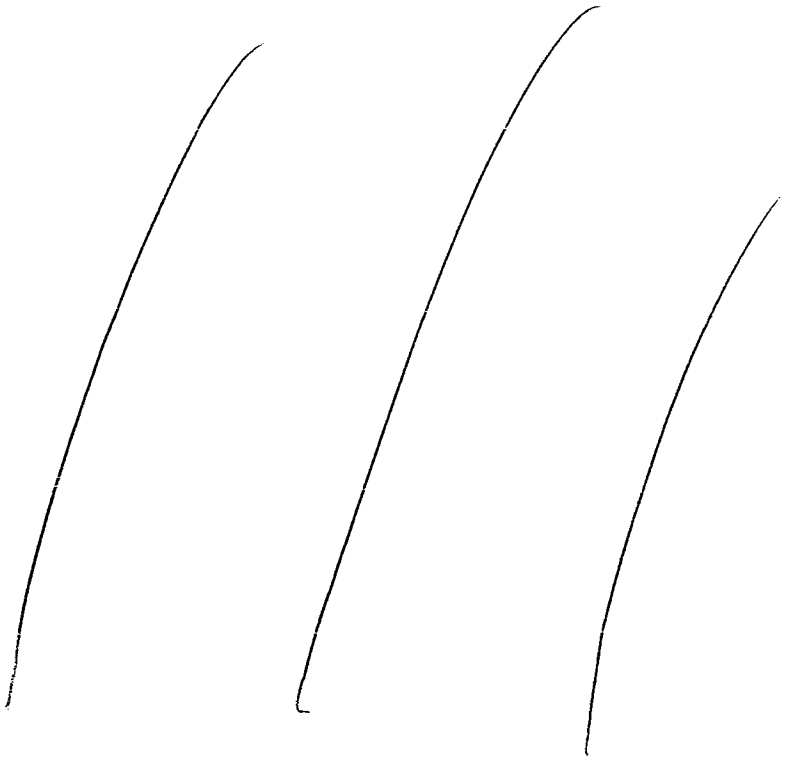
• According to the chemistry team, EMSAM contains a number of impurities/degradants for which insufficient data have been provided to support the sponsor's proposed specifications. Specifically, the concern is in reference to the acceptability of the proposed specifications for 4

in the drug product and one impurity in the drug substance and drug product

Based on currently available information, all of these compounds are suspected to have genotoxic potential. The sponsor should be required to either justify the proposed specifications or, preferably, to lower the specifications consistent with those for other compounds known or suspected to have genotoxic or carcinogenic potential. This issue needs to be addressed prior to approval.

• In order for us to complete our evaluation of the submitted nonclinical data, the sponsor should be asked to provided the following information: (a) clarify the meaning of the abbreviation "TA" in the histopathology tumor data listings and (b) verify that the toxicokinetic data in Table 2 from the 6-month toxicity study in rat, designated as "Selegiline Composite", refers to PK parameters of the parent compound alone.

•The sponsor's proposed labeling needs to be revised as noted below.



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✓ Draft Labeling

_____ Deliberative Process

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/s/

Lois Freed
1/30/04 11:47:39 AM
PHARMACOLOGIST

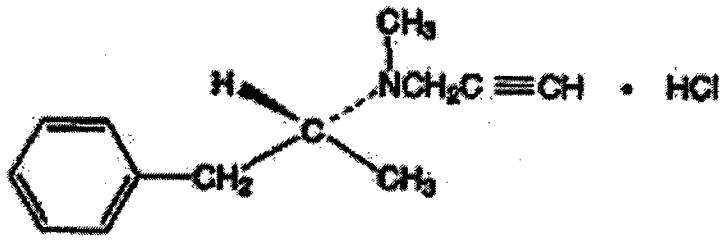
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-336
Review number: 2
Sequence number/date/type of submission: July 31, 2003
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Somerset Pharmaceuticals, Tampa, Florida
Manufacturer for drug substance : [redacted]

Reviewer name: Paul Roney
Division name: Neuropharmacological Drug Products
HFD #: 120
Review completion date: January 28, 2004

Drug:

Trade name: EMSAM
Generic name (list alphabetically): Seligiline Transdermal System
Code name: 1-E-250
Chemical name: R-(-)-N,2-dimethyl-N-2-propynylphenethylamine
CAS registry number: 14611-51-9 (base)
Mole file number:
Molecular formula/molecular weight: $C_{13}H_{17}N$ / 187.28
Structure:



Relevant INDs/NDAs: [redacted], I46,944 (transdermal patch , depression), [redacted], N19-334 (Eldelpryl tablet, Parkinson's disease), N20-647 (Eldepryl capsules, Parkinson's disease)

Drug class: Monoamine oxidase inhibitor (MAOI)

Indication: Treatment of depression

Clinical formulation: Dermal patch containing 20, 30 or 40 mg selegiline

Route of administration: Transdermal Patch

Disclaimer: Tabular and graphical information may be from sponsor's submission

Table of Contents

EXECUTIVE SUMMARY

This is the second review of the preclinical data for NDA 21-336 (Emsam, Selegiline transdermal system for depression). In the previous review, Dr. Freed identified two preclinical issues that the sponsor needed to address:

1. There was inadequate data to assess the genotoxic risk of Selegiline. The sponsor was asked to repeat two genotoxicity studies (Ames assay and in vivo micronucleus test) to allow a full review of the genotoxic potential of Selegiline.
2. There was inadequate data to permit an independent evaluation of the carcinogenic potential of Selegiline in rats and mice. The sponsor was asked to submit electronic datasets to enable an independent review of the carcinogenicity studies in mice and rats.

An additional preclinical concern is the adequacy of the preclinical data to support the higher clinical doses proposed in this submission. In the original NDA submission, the only proposed dose was a 20 mg/20 cm^2 patch. In the present submission, the sponsor proposes additional doses of 30 mg/30 cm^2 and 40 mg/40 cm^2 patches.

The sponsor has performed and submitted the requested genotoxicity studies. The studies were adequately conducted and the results were negative.

The sponsor had previously submitted the electronic datasets, which were reviewed by Ms. Roswitha Kelly. The results of Ms. Kelly's review confirms the Executive Carcinogenicity Committee's concerns that the mouse carcinogenicity study was inadequate due to the short duration of the study (78 weeks versus the recommended 104 week duration) and the incomplete histopathology assessment. It is recommended that the mouse carcinogenicity study be repeated as a phase IV commitment using either a two year study or an appropriate six month study using transgenic mice.

An additional concern is the potential for local dermal toxicity. Selegiline will be administered via a dermal parch which will result in prolonged higher sustained local concentrations of selegiline than would normally occur via oral administration. Since selegiline was positive in the mouse lymphoma assay, the potential for local effects following repeated exposure should be assessed. It is recommended that the sponsor perform a six month dermal study in an appropriate species, such as the minipig, to assess the potential for selegiline to induce preneoplastic lesions. This may be done as a Phase IV commitment.

The repeat dose toxicity studies and the reproductive toxicity studies are adequate to support the higher dose preparations proposed by the sponsor.

This reviewer also recommends some changes to the proposed label as a condition for approval.

If the sponsor agrees to these recommendations, then the preclinical studies are adequate support the Approval of this application.

GENETIC TOXICOLOGY

Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with Selegiline HCl

Study no: **23770-0-409OECD**
Study type (if not reflected in title):
Volume #, and page #: **Section 5, page 7**
Conducting laboratory and location: [redacted]
Date of study initiation: **June 19, 2002**
GLP compliance: **Yes**
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: **9811025**
Formulation/vehicle: **Water**

Methods:

Strains/species/cell line: S. typhimurium TA98, TA100, TA1535, TA1537; E. coli WP2uvrA

Dose selection criteria:

Basis of dose selection: Maximum Recommended Dose

Metabolic activation system: Aroclor 1254 treated male Sprague-Dawley rat liver S9

Controls:

Vehicle: Yes

Positive controls:

Table II. Positive Controls

Tester Strain	S9 Mix	Positive Control	Dose (µg/plate)
TA98	+	benzo[a]pyrene	2.5
TA98	–	2-nitrofluorene	1.0
TA100	+	2-aminoanthracene	2.5
TA100	–	sodium azide	2.0
TA1535	+	2-aminoanthracene	2.5
TA1535	–	sodium azide	2.0
TA1537	+	2-aminoanthracene	2.5
TA1537	–	ICR-191	2.0
WP2*uvr*A	+	2-aminoanthracene	25.0
WP2*uvr*A	–	4-nitroquinoline-N-oxide	1.0

Figure 1, from page 10 of Report 23770-0-409OECD

Exposure conditions:

Incubation and sampling times: 48 hours

Analysis:

No. of replicates: 3 plates/dose; duplicate studies

Counting method:

Criteria for positive results: 2X increase in revertants for TA98, TA100 or E coli WP2uvrA; 3X increase in revertants for TA 1535 and TA1537

Summary of individual study findings:

Study validity: positive control positive; negative controls negative. Adequate doses were used as indicated by cytotoxicity at the higher doses.

Study outcome: Selegiline was negative in this assay.

		Mean Revertants Per Plate with Standard Deviation										Back-ground Lawn[a]
	Dose/Plate	TA98		TA100		TA1535		TA1537		WP2uvrA		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		30	7	84	4	11	3	14	3	18	2	N
Test Article	33.3 µg	24	3	80	10	11	4	12	4	20	5	N
	100 µg	33	1	89	6	13	1	14	9	19	3	N
	333 µg	30	5	58	11	15	1	12	3	13	2	N
	1000 µg	31	10	72	4	10	7	17	3	15	6	N
	3330 µg	24	6	71	5	7	1	8	6	9	4	N/R[d]
	5000 µg	11	16	42	13	11	3	7	1	5	4	N/R[e]
Positive Control[b]		247	20	324	37	108	11	118	10	621	54	N
Microsomes: None												
Vehicle Control		18	5	64	2	16	4	6	4	18	7	N
Test Article	33.3 µg	14	4	93	5	16	1	9	3	14	0	N
	100 µg	10	1	75	5	14	4	14	6	15	3	N
	333 µg	12	4	62	14	18	6	7	1	14	5	N
	1000 µg	16	5	69	9	20	3	9	2	15	5	N
	3330 µg	15	2	74	21	13	3	4	2	5	4	N/R[f]
	5000 µg	0	-	30	27	8	6	0	0	3	3	N/R[e]
Positive Control[c]		126	27	1022	110	744	35	758	74	149	23	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b] TA98	benzo[a]pyrene	2.5 µg/plate	[c] TA98	2-nitrofluorene	1.0 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate	TA100	sodium azide	2.0 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate	TA1535	sodium azide	2.0 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate	TA1537	ICR-191	2.0 µg/plate
WP2uvrA	2-aminoanthracene	25.0 µg/plate	WP2uvrA	4-nitroquinolone-N-oxide	1.0 µg/plate

[d] The first entry is the lawn evaluation for tester strains TA98, TA100, and WP2uvrA.
The second entry is the lawn evaluation for tester strains TA1535 and TA1537.
[e] The first entry is the lawn evaluation for tester strain WP2uvrA.
The second entry is the lawn evaluation for tester strains TA98, TA100, TA1535, and TA1537.
[f] The first entry is the lawn evaluation for tester strains TA98, TA100, TA1535, and WP2uvrA.
The second entry is the lawn evaluation for tester strain TA1537.

Figure 2, from page 21 of Report 23770-0-409OECD

	Dose/Plate	Mean Revertants Per Plate with Standard Deviation										Back-ground Lawn[a]
		TA98		TA100		TA1535		TA1537		WP2*uvr*A		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		27	7	76	5	10	2	9	3	12	3	N
Test Article	33.3 µg	29	6	82	3	16	5	9	4	13	4	N
	100 µg	24	9	79	6	16	4	9	4	18	5	N
	333 µg	21	1	75	13	11	1	12	4	14	7	N
	1000 µg	30	5	82	9	11	2	11	6	5	3	N
	3330 µg	33	4	57	5	9	1	9	1	6	1	N/R[d]
	5000 µg	12	5	33	12	9	3	3	3	3	0	N/R[e]
Positive Control[b]		301	40	347	38	97	12	96	6	612	183	N
Microsomes: None												
Vehicle Control		13	4	74	7	10	2	11	6	12	1	N
Test Article	33.3 µg	14	5	79	6	11	2	9	5	14	3	N
	100 µg	11	1	78	10	12	4	6	1	14	5	N
	333 µg	10	8	68	5	10	2	6	3	14	2	N
	1000 µg	10	3	73	6	20	4	4	1	8	3	N
	3330 µg	8	2	47	7	16	5	8	1	4	1	N/R[f]
	5000 µg	5	1	22	9	6	3	0	0	1	1	N/R[e]
Positive Control[c]		347	48	930	118	705	13	1720	290	110	20	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b] TA98	benzo[a]pyrene	2.5 µg/plate	[c] TA98	2-nitrofluorene	1.0 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate	TA100	sodium azide	2.0 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate	TA1535	sodium azide	2.0 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate	TA1537	ICR-191	2.0 µg/plate
WP2*uvr*A	2-aminoanthracene	25.0 µg/plate	WP2*uvr*A	4-nitroquinolone-N-oxide	1.0 µg/plate

[d] The first entry is the lawn evaluation for tester strains TA98, TA1535, TA1537, and WP2*uvr*A.
The second entry is the lawn evaluation for tester strain TA100.
[e] The first entry is the lawn evaluation for tester strain WP2*uvr*A.
The second entry is the lawn evaluation for tester strains TA98, TA100, TA1535, and TA1537.
[f] The first entry is the lawn evaluation for tester strains TA1535, TA1537, and WP2*uvr*A.
The second entry is the lawn evaluation for tester strainS TA98 and TA100.

Figure 3, from page 23 of Report 23770-0-409OECD

In Vivo Mouse Micronucleus Assay with Selegiline HCl

Study no: **23770-0-455OECD**
Study type (if not reflected in title):
Volume #, and page #: **Section 5, page 7**
Conducting laboratory and location: [redacted]
Date of study initiation: **June 25, 2002**
GLP compliance: **Yes**
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: **9811025**
Formulation/vehicle: **Water,** [redacted]

Methods:

Strains/species/cell line: Mouse, CD-1(ICR) BR, males only.
Dose selection criteria:
Basis of dose selection: Maximum Tolerated Dose
Range finding studies: 3/6 mice died at 400 mg/kg
Test agent stability:
Metabolic activation system: NA
Controls:
Vehicle: Yes
Positive controls: 80 mg/kg cyclophosphamide
Exposure conditions:
Incubation and sampling times: 24 hours (all doses), 48 hours (0, 200 mg/kg only)
Doses used in definitive study: 50, 100, 200 mg/kg
Analysis:
No. of replicates: 5 mice/dose/timepoint; 2000 PCE/mouse
Criteria for positive results: statistically significant increase in micronuclei

Key findings:

Study validity: positive control positive, negative control negative, adequate doses were used based on mortality at 400 mg/kg.

Study outcome:

Selegiline did not cause a statistically significant increase in micronuclei.

TABLE 1: MICRONUCLEUS DATA SUMMARY TABLE

ASSAY NO.: 23770
TEST ARTICLE: Selegiline HCl

TREATMENT	DOSE	HARVEST TIME	% MICRONUCLEATED PCEs MEAN OF 2000 PER ANIMAL ± S.E. MALES	RATIO PCE:NCE MEAN ± S.E. MALES
CONTROLS				
VEHICLE	Cell Culture Grade Water	24 hr	0.02 ± 0.01	0.45 ± 0.07
		48 hr	0.04 ± 0.01	0.69 ± 0.10
POSITIVE	CP 80mg/kg	24 hr	2.87 ± 0.33*	0.57 ± 0.04
TEST ARTICLE	50mg/kg	24 hr	0.01 ± 0.01	0.61 ± 0.07
	100mg/kg	24 hr	0.06 ± 0.02	0.47 ± 0.04
	200mg/kg	24 hr	0.03 ± 0.01	0.59 ± 0.05
		48 hr	0.08 ± 0.03	0.50 ± 0.05

* Significantly greater than the corresponding vehicle control, $p \leq 0.01$.
CP = Cyclophosphamide
PCE = Polychromatic erythrocyte
NCE = Normochromatic erythrocyte

Figure 4, from page 17 of Report 23770-0-455OECD

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ON ORIGINAL

HISTORICAL CONTROL DATA

Mouse Micronucleus - 1/2000 Through 12/2000

		% MICRONUCLEATED PCEs FROM 2000 PCES PER ANIMAL MEAN ± S.E. *MALES*	PCE:NCE RATIO MEAN ± S.E. *MALES*
POOLED VEHICLE CONTROLS			
24 hour harvest	Minimum	0.00	0.20
	Maximum	0.35	3.85
	Average	0.062± 0.004	0.867 ± 0.038
	N	225	225
48 hour harvest	Minimum	0.00	0.17
	Maximum	0.35	2.60
	Average	0.068 ± 0.005	0.777 ± 0.030
	N	170	170
POSITIVE CONTROLS Cyclophosphamide, 80.0 mg/kg			
24 hour harvest	Minimum	0.20	0.18
	Maximum	6.40	3.10
	Average	2.412 ± 0.083	0.737± 0.027
	N	220	220

PCE = Polychromatic erythrocyte
NCE = Normochromatic erythrocyte
N = Number of animals

Figure 5, from page 20 of Report 23770-0-455OECD

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OVERALL SUMMARY AND CONCLUSIONS

Drug History

Selegiline is a monoamine oxidase inhibitor which is approved for the treatment of Parkinson's disease as an oral formulation. In this NDA, the sponsor is proposing that a transdermal selegiline patch containing 20, 30 or 40 mg selegiline is safe and effective for the treatment of depression. This NDA was originally submitted on May 25, 2001, but it was judged Not Approvable by the Division due to a lack of proof of clinical efficacy. The original NDA was only for a 20 mg selgiline patch; the current NDA includes 30 and 40 mg patches. The preclinical data were reviewed by Dr. Lois Freed (review dated March 1, 2002) under the assumption that the maximum daily dose would be a 20 mg transdermal patch. Dr Freed recommended that the NDA not be approved due to an inadequate assessment of carcinogenic potential. The basis for this conclusion was that the sponsor had not provided electronic datasets for the results of the mouse and rat carcinogenicity studies. The Division discussed this issue with the sponsor on January 30, 2002. The sponsor agreed to provide the datasets, but noted that they would not be able to provide the March 25, 2002 action date on the original NDA. The Division assured the sponsor that the Division would not initiate a nonapproval action based on the lack of datasets. The sponsor submitted the electronic datasets on May 21, 2002. The data were subsequently analyzed by Ms Roswitha Kelly. Dr. Freed also recommended that the sponsor repeat two genotoxicity studies: the Ames assay and the in vivo cytogenetics assay. The sponsor submitted the genotoxicity studies with this NDA on July 31, 2003.

Since the preclinical data have been previously reviewed (see page 17 for Dr Freed's summary of the preclinical data), this review will examine the issues identified in her original review. This review will also examine the adequacy of the preclinical data to support the use of the 30 and 40 mg transdermal patches. For comparisons of animal and human doses, it is assumed that the daily dose from the 40 mg transdermal patch is 12 mg/day (as per Dr. Kavanagh's review, page 10). Dr. Freed's notes that, according to the sponsor, a dermal rat dose of 120 mg/kg/day is equivalent to an absorbed dose of 24 mg/kg/day (page 49 of her review). No data on absorbed rabbit doses were available.

Genotoxicity Studies

In the original Ames assay, selegiline was tested at a high dose of 50 ug/plate in the absence of metabolic activation (S9) and 500 ug/plate in the presence of metabolic activation. However, no cytotoxicity was observed in this study and the doses were below the recommended limit dose of 5000 ug/plate. In the repeat study, selegiline was tested in four strains of Salmonella typhimurium (TA98, TA100, TA1535 and TA1537) and one strain of Escherichia coli (WP2 uvrA) at doses up to 5000 ug/plate in the presence and absence of metabolic activation. Cytotoxicity (decreased revertant counts or reduced background lawn) was observed in all strains except TA1535 in the absence of metabolic activation. Cytotoxcity was also observed at 3300 ug/plate in S. typhimurium TA1537 and E. coli WP2 uvrA. No significant increase in the incidence of revertants was observed in selegiline treated bacteria. This study is adequate to address the potential for selegiline to induce mutations in bacterial systems.

The original in vivo genotoxicity test was performed by a laboratory which had conducted deficient genotoxicity studies on selegiline. It was decided that it would be prudent to request the sponsor to repeat the in vivo genotoxicity study. In the repeat study, mice (5 males/dose/time point) were administered 0, 50, 100 or 200 mg/kg selegiline and their bone marrow were examined for micronuclei formation 24 and 48 (0, 200 mg/kg only) hours later. No significant increase in micronuclei formation was observed. The high dose was considered adequate based on mortality observed at 400 mg/kg (3/6 mice died after administration). This study is adequate to address the potential for selegiline to induce genotoxicity in vivo.

It is concluded that the genotoxic potential of selegiline has been adequately examined. Based in part on Dr. Freed's review, Selegiline is positive in the mouse lymphoma assay, but negative in the Ames assay, chromosomal aberrations assay in human lymphocytes and the in vivo micronucleus test.

Carcinogenicity Studies

The major preclincial issue is the adequacy of the mouse carcinogenicity study.

In the mouse carcinogenicity study, seleginiline was administered in the diet at projected doses of 0, 3, 10 and 30 mg/kg/day for 78 weeks. The duration of this study is much shorter than what is considered an adequate study duration (104 weeks). In addition, the study had incomplete histopathology. The following tissues were not examined: duodenum, jejunum, cecum, rectum, eye, harderian gland, lacrimal gland, larynx, cervical or mandibular lymph nodes, nasal cavity, optic nerves, peripheral nerve, pharynx, seminal vesicles, skeletal muscle, spinal cord, vagina/cervix, zymbal gland. No statistically significant increase in neoplasms was observed in this study. However, by design, this study had relatively low sensitivity to detect carcinogenicity due to limited duration and incomplete histopathology. On January 8, 2002, the Executive Carcinogenicity Assessment Committee (Exec CAC) reviewed this study and concluded that the study was "inadequate based on the short duration and the lack of a complete battery of tissues examined for histopathology." (see page 19 for complete minutes). The study would have been considered acceptable if the independent review of the carcinogenicity study datasets had suggested that the study had actually detected a statistically significant increase in tumors. However ,the independent review did not detect any increase in tumors (see page 19 for executive summary of Ms Kelly's statistical review). Based on these considerations, it is concluded that the carcinogenic potential of selegiline has not been adequately assessed in the mouse. This is particularly a concern since selegiline was positive in in vitro genotoxicity assays and the drug will be given to a relatively young group of patients (patients with depression) as opposed to the currently approved use (Parkinson's disease). It is recommended that either a two year or an alternative carcinogenicity study be conducted in the mouse. This can be a Phase IV commitment.

This reviewer is concerned about the potential of selegiline to cause a local neoplastic effects. Selegiline was positive in the mouse lymphoma assay and the dermal route of exposure will result in sustained high concentrations of the drug at the site of exposure. Since depression is a chronic disorder with a significant portion of the potential population being young, there is appreciable concern about the potential carcinogenicity of the drug substance. It is therefore recommended that the sponsor conduct a six month dermal study using an appropriate animal model, such as the minipig, to assess the potential for selegiline to induce preneoplastic foci. This may be done as a Phase IV commitment.

Adequacy of Preclinical Studies to Support Higher Clinical Doses

Dr. Freed's original NDA review assumed that the Maximum Recommended Human Dose (MRHD) would be a 20 mg/20 cm^2 patch. However, the current NDA is proposing a MRHD of 40 mg/40 cm^2 patch. This will result in higher circulating levels of Selegiline than was originally assumed when the original NDA was reviewed. Dr. Freed has concluded that the preclinical studies were adequately performed (except for the carcinogenicity and genotoxicity studies noted above). This reviewer will not examine these studies in detail but will focus on the level of circulating Selegiline and metabolites.

Dr Ron Kavanagh has reviewed the pharmacokinetics of transdermal Selegiline (review dated January 14, 2004). The steady state concentration of Selegiline was reasonably constant over 24 hours, so the predose concentration (concentration 30 minutes prior to the administration of a new patch) are a reasonable estimate of exposure over a 24 hour period. The circulating levels of Selegiline and its metabolites are presented below.

Table 12 Mean Steady-State Predose Concentrations and Metabolite : Selegiline Ratios by Dosage – (Study PE158)

Selegiline Treatment	N	Selegiline Concentration (ng/ml)	Desmethylselegiline Concentration (ng/ml)	Methamphetamine Concentration (ng/ml)	Amphetamine Concentration (ng/ml)	Ratio of Desmethyl-selegiline : Selegiline	Ratio of Meth-amphetamine : Selegiline	Ratio of Amphetamine : Selegiline
20 mg qd 1 x 20 mg / 20 cm^2	8	2.0 ± 0.3 (15.8) [1.9] 1.6 - 2.4	1.8 ± 0.2 (22.5) [1.8] 0.7 - 1.4	5.5 ± 1.5 (27.2) [5.4] 4.0 - 8.1	2.1 ± 0.5 (23.8) [2.0] 1.5 - 3.1	0.51 ± 0.10 (19.6) [0.53] 0.35 - 0.67	2.88 ± 0.92 (31.8) [2.83] 1.80 - 4.26	1.09 ± 0.25 (23.0) [1.01] 0.85 - 1.63
30 qd 1 x 30 mg / 30 cm^2	8	3.8 ± 0.9 (24.5) [3.7] 2.8 - 5.9	2.7 ± 1.2 (43.9) [2.3] 1.7 - 5.3	12.0 ± 3.5 (28.9) [11.1] 8.1 - 17.1	4.6 ± 1.1 (24.1) [4.7] 3.0 - 6.2	0.70 ± 0.24 (34.1) [0.65] 0.43 - 1.21	3.17 ± 0.89 (28.2) [2.78] 2.42 - 4.63	1.19 ± 0.22 (18.2) [1.14] 0.91 - 1.55
40 qd 2 x 20 mg / 20 cm^2	8	4.5 ± 1.4 (30.3) [4.5] 1.9 - 6.5	3.1 ± 1.1 (34.1) [2.8] 2.1 - 5.5	13.4 ± 3.7 (27.5) [13.9] 8.3 - 18.9	5.2 ± 1.4 (26.5) [5.0] 3.1 - 7.4	0.74 ± 0.35 (47.3) [0.61] 0.46 - 1.35	3.04 ± 0.74 (24.2) [3.00] 1.85 - 4.32	1.23 ± 0.53 (43.1) [1.15] 0.64 - 2.44

Figure 6, from page 64 of Dr. Kavanagh's January 14, 2004 Review

In the chronic toxicity studies, rats were administered dermal patches containing 0, 30, 60 or 120 mg/kg/day for six months. In the chronic dog study, dogs were administered dermal patches containing 0, 6, 12 or 24 mg/kg/day for nine months. The primary toxicity observed was body weight loss and local dermal irritation; increased ALT levels were also observed in high dose dogs. Dr. Freed concluded that "Although no serious drug-related toxicities were observed at the HD (high dose), the MD (mid dose) could be considered a NOAEL due to increases in ALT and some clinical signs at the HD." (page 49). This reviewer concurs with this conclusion. A comparison of plasma levels of selegiline and its metabolites to human levels is presented below.

Selegiline and metabolite concentrations (ratio to human steady state concentration) in chronic toxicity studies.

Species	Endpoint	Selegiline Concentration (ng/ml)	Desmethylselegiline Concentration (ng/ml)	Methamphetamine Concentration (ng/ml)	Amphetamine Concentration (ng/ml)
Human		4.6	3.1	13.4	5.2
Rat	NOEL	22.9 (5.0)	5.42 (1.7)	5.69 (0.4)	5.81 (1.1)
	LOEL	48.9 (10.6)	8.74 (2.8)	13.1 (1.0)	13.5 (2.6)
Dog	NOEL	12.3 (2.7)	2.94 (0.9)	10.8 (0.8)	48.2 (9.3)
	LOEL	24.8 (5.4)	3.72 (1.2)	15.6 (1.2)	81.0 (15.6)

The plasma levels in the preclinical species were generally higher than the levels observed in the clinic. The metabolite concentrations were generally comparable to the clinical situation. This suggests that the preclinical studies were adequate models.

A separate evaluation was examined for the reproductive toxicity studies. In the Segment I, II and III studies, rats were administered dermal patches containing 0, 10, 30 and 75 mg/kg selegiline. Toxicokinetic parameters were not evaluated in the Segment I study, but they were evaluated in the Segment II and III studies. In the Segment I study, the LOEL was 75 mg/kg (based on adverse effects on sperm parameters) and the NOEL was 30 mg/kg. In the Segment II study, the LOEL was 75 mg/kg (based on increased visceral and total malformations) and the NOEL was 30 mg/kg. In the Segment III study, the LOEL was 10 mg/kg (based on delays in developmental parameters) and a NOEL was not established.

In the Segment II rabbit study, rabbits were administered dermal patches containing 0, 2.5, 10 and 40 mg/kg selegiline. The reproductive LOEL was 40 mg/kg (based on increases in visceral malformations and skeletal variations) and the NOEL was 10 mg/kg. The ratios of parent and metabolites is presented below.

Selegiline and metabolite concentrations (ratio to human steady state concentration) in reproductive toxicity studies.

Species	Endpoint	Selegiline Concentration (ng/ml)	Desmethylselegiline Concentration (ng/ml)	Methamphetamine Concentration (ng/ml)	Amphetamine Concentration (ng/ml)
Human		4.6	3.1	13.4	5.2
Rat	10	3.34 (0.7)	1.02 (0.3)	2.3 (0.2)	1.9 (0.4)
	30	18.1 (3.9)	4.62 (1.5)	11.2 (0.8)	8.06 (1.6)
	75	42.5 (9.2)	12.6 (4.1)	32 (2.4)	18.5 (3.6)
Rabbit	10	4.84 (1.1)	8.99 (2.9)	2.79 (0.2)	2.98 (0.6)
	40	42.4 (9.2)	47.7 (15.4)	10.6 (0.8)	11.1 (2.1)

These data suggest that the animals were exposed to higher plasma levels of selegiline and its metabolites than would occur in the clinical setting. Based on Dr Freed's review, the doses used in these studies were adequate to evaluate the potential reproductive toxicity of Selegiline.

It is concluded that the preclinical chronic toxicity and reproductive toxicity studies are sufficient to support the increase in the MRHD from the 20 mg patch to the 40 mg patch. The changes in the MRHD should be reflected in the Sponsor's proposed label.

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RECOMMENDATIONS

The available preclinical data are sufficient to support the approval of this NDA. Nevertheless, there are data gaps that the sponsor will need to address in Phase IV commitments.

1. The mouse carcinogenicity is inadequate due to its short duration and incomplete histopathological assessment. The sponsor will need to conduct either a two year or an alternative carcinogenicity study.
2. Since selegiline is genotoxic, the potential carcinogenicity of selegiline should be further examined in a six month preneoplastic dermal study using an appropriate animal species (e.g., minipig).
3. The proposed labeling changes outlined outlined starting on page 22 should be implemented.

APPENDIX 1: EXECUTIVE SUMMARY OF DR FREED'S NDA REVIEW

Executive Summary

I. Recommendations

A. Recommendation on Approvability:

From a pharmacology/toxicology standpoint, it is recommended that this NDA not be approved due to the lack of adequate assessment of carcinogenic potential. Specifically, the sponsor has not provided the data for either the mouse or rat carcinogenicity studies in a format that will allow for independent review of the results. The sponsor has committed to providing electronic datasets for the studies; however, they have not been received.

B. Recommendation for Nonclinical Studies:

Although not a basis for the nonapprovable recommendation, the sponsor needs to provide additional information regarding the genotoxic potential of selegiline STS.

The following information should be relayed to the sponsor:

Regarding the genotoxicity studies, you should conduct a repeat Ames test using concentrations of selegiline sufficient to produce cytotoxicity in each tester strain, with and without metabolic activation. You should also conduct a repeat *in vivo* cytogenetics assay unless you can provide (a) justification for the use of the oral route to support your transdermal formulation and (b) documentation that the study was conducted adequately. You have stated that the mouse lymphoma assay and the *in vitro* chromosomal aberration assay conducted by [redacted] were invalid due to serious methodological problems. The *in vivo* cytogenetics assay was also conducted by [redacted] therefore, we need additional assurance that this study was adequately conducted. If you cannot provide justification that the oral route is adequate to support the transdermal route, then a repeat assay should be conducted (using an appropriate route) and no additional validation of the *in vivo* cytogenetics assay would be necessary.

C. Recommendations on Labeling: none.

II. Summary of Nonclinical Findings

Selegiline has been demonstrated to be an MAO inhibitor, with selectivity for MAO-B following low-dose oral administration. At higher plasma exposures achieved with transdermal delivery, selegiline was shown to equally inhibit MAO-A and MAO-B in rat brain [and cardiac tissue], while maintaining some selectivity for MAO-B over MAO-A in intestine. Based on these findings, the sponsor concluded that selegiline administered transdermally would result in sufficient inhibition of MAO-A to exert an antidepressant effect while minimizing the risk of a hypertensive reaction.

The primary findings in the chronic transdermal toxicity studies conducted in rat and dog were adverse effects on body weight and local irritation. Local irritation was observed even in control animals receiving the patch; however, there was evidence in some studies of drug-related irritation. Selegiline STS had no effects on mating and fertility in rats; however, sperm concentration and total count were reduced suggesting a possible adverse effect on male fertility. In embryofetal development studies in rat and rabbit, selegiline STS was associated with adverse fetal effects, including decreases in fetal body wt (in rat), an increased incidence of visceral

Figure 7, from page 3 of Dr. L. Freed Review

malformations in both species and an increased incidence of total malformations in rat; no pattern of malformations was observed. Selegiline STS also exerted adverse effects on peri/postnatal development, resulting in reduced pup survival at birth and throughout the lactation period and delays in achieving developmental milestones. In addition, there was a decrease in litter size in the F_1 generation assessed for reproductive performance. No-effect levels were established for all but developmental delays.

The oral carcinogenicity studies conducted in mouse and rat could not be completely evaluated due to the lack of data in a format that would allow for independent evaluation. Based on the review of the data in the available format, it would appear that additional assessment is needed, at least in the mouse. However, a final decision as to the need for additional assessment of carcinogenic potential await the sponsor's submission of datasets and review of those data. Factors that must be considered in making a final determination include, in addition to the results of the statistical analysis, the adequacy of plasma drug levels achieved in the oral carcinogenicity studies relative to those in humans at the maximum clinical dose (particularly if the sponsor pursues higher clinical doses) and, possibly, the need to assess local dermal effects.

Numerous genotoxicity studies were conducted, however, they do not provide an adequate assessment of genotoxicity. The Ames test was negative, but was inadequate due to the lack of any evidence of cytotoxicity for the majority of tester strains tested. The *in vivo* micronucleus assay, also negative, needs additional data justifying the use of the oral route to support a transdermal formulation and documentation that the study was conducted using valid methodology. Selegiline produced increases in small and large colonies (indicative of clastogenic and mutagenic effects) in 2 separate mouse lymphoma assays [the sponsor considered one assay invalid]. Two *in vitro* chromosomal aberration assays in human lymphocytes were conducted; one was positive [the sponsor considered this assay invalid] and a repeat study was negative.

Figure 8, from page 4 of Dr. L. Freed's Review

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APPENDIX 2: EXECUTIVE SUMMARY OF MS. KELLY'S REVIEW

1 Executive Summary

1.1 Conclusions

In this reviewer's opinion, the validity of the rat study is in question. The treatment with selegiline HCl did not produce any increase in mortality or tumor incidences. On the contrary, the high dose animals of both genders had consistently **lower** tumor rates than any other treatment group including the controls. In addition, the mean body weights of the high dose groups were greatly reduced compared to the controls. The length of exposure and the number of animals exposed to treatment were acceptable. However, the very low mean body weights of the high dose rats may have affected tumor development and therefore the lack of any increase in tumor incidences may not reflect a true lack of carcinogenic potential of selegiline HCl.

The validity of the mouse study is even more questionable. It suffered from the same shortcomings as the rat study, namely very low tumor rates and greatly reduced mean body weights of the high dose animals of both genders compared to the controls. In addition, the study lasted only 78 weeks, which may be too short to permit formation of late developing tumors. From the statistical perspective, a carcinogenic potential of selegiline HCl cannot be ruled out despite any increases in tumor findings.

Finally, it is noted that the route of administration is not identical between the rodent bioassays (oral dietary) and the human use (transdermal) in this application.

1.2 Overview of Studies Reviewed

One rat and one mouse bioassay was reviewed. Both studies had been previously submitted to NDA 20-647. However at that time full microscopic histopathology had been done only for the control and high dose animals, for some target organs of all animals and for the low and mid dose animals dying on study. The sponsor had been requested to provide the tumor data for all tissues from all animals. In addition, the sponsor performed a peer review on some of the previous and new findings. Therefore, a new statistical review was warranted.

1.3 Principal Findings

Selegiline HCl was administered in the diet for 104 weeks to Sprague Dawley rats in doses up to 17.5mg/kg/day. Survival was not affected by the administration of the compound and no increase in tumor incidences was observed. However, selegiline had a major effect on reducing mean body weights of the high dose animals. As a matter of fact, the frequency of tumors among the high dose animals was generally lower than the frequency of any other treatment group, including the controls. Excluding the high dose rats from analysis showed numeric increases in some tumors among both the females and males, but p-values at best approached statistical significance.

Figure 9, from page 4 of Ms. R. Kelly's Review

Selegiline HCl was administered in the diet for 78 weeks to CD-1 mice in doses up to 30.0mg/kg/day. As with the rat study, survival among the mice was not affected by the administration of the compound and no increase in tumor incidences was observed. However, selegiline had a major effect on reducing mean body weights of the high dose animals. As a matter of fact, the frequency of tumors among the high dose animals was generally lower than the frequency of any other treatment group, including the controls. Excluding the high dose animals from analysis did not result in any statistically significant or approximately significant findings. Another major concern for the mouse study is its brevity. Seventy-eight weeks may have been too short a duration to allow for the formation of late developing tumors.

Figure 10, from page 5 of Ms. R. Kelly's Review

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APPENDIX 3: EXECUTIVE CAC MEETING MINUTES

Executive CAC
Date of Meeting
Mouse/Rat Carcinogenicity Study

Committee: Joseph Contrera, Ph.D., HFD-900, Chair
Robert Osterberg, HFD-520, Member
John Leighton, HFD-150, Alternate Member
Barry N. Rosloff, Ph.D., HFD-120, Supervisor
Lois M. Freed, Ph.D., HFD-120, Presenting Reviewer

Author of Draft: Lois M. Freed, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND/NDA #21-336
Drug Name: selegiline transdermal system
Sponsor: Somerset Pharmaceuticals, Inc.

Mouse Carcinogenicity Study: the committee concurred with the reviewer that the 78-wk dietary study was inadequate based on the short duration and the lack of a complete battery of tissues examined for histopathology. The committee also agreed that assay sensitivity may have been reduced at the HD due to the excessive body wt effect (the only dose-limiting effect) observed.

Rat Carcinogenicity Study: the committee concurred with the reviewer that: (a) the 104-wk dietary carcinogenicity study in rat was deficient in that a complete battery of tissues was not examined for histopathology, (b) assay sensitivity may have been reduced at the HD due to the excessive body wt effect observed; however, adequate assay sensitivity was achieved by examination of the lower doses.

Executive CAC Recommendations and Conclusions: the committee concluded that the carcinogenic potential of selegiline had not been adequately assessed. Adequate assessment of the carcinogenic potential is of particular concern because of selegiline's positive genotoxicity findings. It was recommended that either a 2-yr or an alternative carcinogenicity study (e.g., TG.AC, p53) be conducted in mouse. The sponsor should provide justification for the assay selected.

Joseph Contrera, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-120
/BNRosloff, HFD-120
/LMFreed, HFD-120
/DBates, HFD-120
/ASeifried, HFD-024

26 Page(s) Withheld

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✓ Draft Labeling

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/s/

Paul Roney
1/28/04 04:31:10 PM
PHARMACOLOGIST

Lois Freed
1/29/04 07:07:07 AM
PHARMACOLOGIST
Please see my memo (dated 1/29/04) for comments and discussion.

PHARMACOLOGY/TOXICOLOGY MEMORANDUM TO NDA 21-336

Date: 6/6/02
Drug: selegiline transdermal system [STS]
Sponsor: Somerset Pharmaceuticals, Inc.
Indication: major depression
Re: sponsor's Amendment [N-BP, 5/15/02].

Background: In the review of NDA 21-336 [Review and Evaluation of Pharmacology/Toxicology Data, Lois. M. Freed, Ph.D., 3/1/02], it was recommended that the following information be relayed to the sponsor:

> "Regarding the genotoxicity studies, you should conduct a repeat Ames test using concentrations of selegiline sufficient to produce cytotoxicity in each tester strain, with and without metabolic activation. You should also conduct a repeat *in vivo* cytogenetics assay unless you can provide (a) justification for the use of the oral route to support your transdermal formulation and (b) documentation that the study was conducted adequately. You have stated that the mouse lymphoma assay and the *in vitro* chromosomal aberration assay conducted by ——— were invalid due to serious methodological problems. The *in vivo* cytogenetics assay was also conducted by ——— therefore, we need additional assurance that this study was adequately conducted. If you cannot provide justification that the oral route is adequate to support the transdermal route, then a repeat assay should be conducted (using an appropriate route) and no additional validation of the *in vivo* cytogenetics assays would be necessary."

The sponsor has responded by submitting protocols for repeat Ames and *in vivo* cytogenetics assays.

Comment: the Division is not in the practice of providing feedback on routine toxicity studies. The sponsor should be referred to the OECD guidelines and the ICH guidances on genotoxicity testing [i.e., Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals, ICH-S2A (Apr 1996); A Standard Battery for Genotoxicity Testing of Pharmaceuticals, ICH-S2B (Jul 1997)].

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/s/

Lois Freed
6/10/02 02:47:29 PM
PHARMACOLOGIST

Barry Rosloff
7/23/02 12:25:25 PM
PHARMACOLOGIST

Barry N. Rosloff, Ph.D.
3/25/02

NDA 21-336 (Selegiline transdermal)
Supervisory Memo to File

I concur with the recommendations made in Dr. Freed's review of 3/1/02 (noting that the Division has decided that although the carcinogenicity datasets will eventually be needed, the lack of submission of such datasets would not be a basis for a non-approvable action in the current review cycle (which ends today).

As Dr. Freed indicates, a final decision on the adequacy of the carcinogenicity studies should await submission of the datasets (which are needed for independent statistical evaluation). Problems with the carcinogenicity studies identified in the review include (1) the duration of the mouse study was only 78 weeks, (2) several tissues normally evaluated histologically were not so examined in either the rat or mouse study, and (3) estimated exposure in the rat study was relatively low (similar to humans for parent compound [although greater than humans for metabolites]), and (4) no data on exposure in mice were presented. However, it should be noted that prior to Dr. Freed's review of these issues, the question of exposure had already been addressed by the Division, and it was decided, at least regarding systemic exposure, that the oral carcinogenicity studies would be adequate to support the human transdermal formulation. (This was transmitted to the sponsor at the meeting of 3/28/01). (The primary basis for this conclusion was that although human plasma levels of parent compound are several fold greater with transdermal than with oral dosing, levels of 3 structurally and/or pharmacologically related metabolites, and combined levels of parent drug and these metabolites, are lower with transdermal dosing. [However, note that the sponsor is apparently intending to study higher doses of transdermal selegiline, which will necessitate eventual re-visiting of this issue]).

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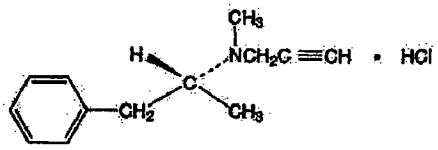
/s/

Barry Rosloff
3/25/02 03:09:20 PM
PHARMACOLOGIST

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Reviewer Name: Lois M. Freed, Ph.D.
Division Name: Neuropharmacological Drug Products
HFD#120
Review Completion Date: 03/01/02
Review number: 1
NDA number: **21-336**
Serial number/date: original application, 5/25/01
Information to sponsor: Y
Sponsor (or agent): Somerset Pharmaceuticals, Inc.
2202 North West Shore Boulevard
Suite 450
Tampa, FL33607
Manufacturer for drug substance:

Drug: Selegiline Transdermal System
Code Name: 1-E-250
Generic Name: n/a
Trade Name: EMSAM
Chemical Name: [R-(-)-N,α-dimethyl-N-2-propynlphenethylamine]
CAS Registry Number: CAS-14611-51-9 (base)
Molecular Weight: 187.28
Structure:



Relevant INDs/NDAs/DMFs:
, I46944 [selegiline t.d.; Somerset Pharmaceuticals Inc., depression],
, N19-334 [Eldelpryl tablet, Somerset Pharmaceuticals Inc., Parkinson's disease], N20-647 [Eldepryl capsules, Somerset Pharmaceuticals Inc., Parkinson's disease].
Drug Class: irreversible MAO-B inhibitor
Indication: depression
Clinical formulation: transdermal deliver system. Rectangular in shape, with dimensions of 44.25 x 50.80 mm. Three main components: drug delivery adhesive matrix, backing film, and protective release liner. The drug deliver adhesive matrix contains selegiline base [20 mg/20 cm^2] "...dispersed in a adhesive . The backing film is a material ...The release liner is a [that] is discarded prior to application..." The final drug product is comprised of 20 mg of selegiline base.

Route of administration: transdermal
Studies reviewed within this submission:

Pharmacology (Vol 1.006-1.009;)
PK/ADME (Vol 1.048-1.069;eSection 5D)
Report 19 [eSection 5C]: 14-day dietary PK study
Toxicology (Vol 1.010-1.046; eSection 5C)
Report 02: 21-day t.d. range-finding toxicity study, rat
Report 03: 6-mo t.d. toxicity study, rat
Report 04: 9-mo t.d. toxicity study, dog
Report 05: 21-day p.o. (gavage) range-finding toxicity study, rat
Report 06: non-regulated t.d. feasibility study, rat
Reproduction (Vol; eSection 5C)
Report 07: Segment I t.d. study, rat
Report 08: range-finding t.d. Segment II study, rat
Report 09: Segment II t.d. study, rat
Report 10: Segment III t.d. study, rat
Report 11: range-finding t.d. Segment II study, rabbit
Report 12: Segment II t.d. study, rabbit
Genotoxicity (Vol 1.045-1.046; eSection 5C)
Report 13: Ames test
Report 14: mouse lymphoma assay
Report 15: mouse lymphoma assay
Report 16: *in vitro* chromosomal aberration in human lymphocytes
Report 17: *in vitro* mammalian chromosomal aberration assay
Report 18: *in vivo* cytogenetics test, mouse
Published literature (Vol; eSection 5E)

Studies not reviewed within this submission: none

Review history:[Studies to support selegiline transdermal were conducted under [redacted], I46944, [redacted], all held by Somerset.]

Pharmacologist Review of [redacted] [Barry N. Rosloff, Ph.D., 6/10/93]: acute primary dermal irritation in rabbits, 4-wk repeat dose dermal irritation in rabbits, dermal sensitization in guinea pigs, acute i.v. toxicity in [redacted] rats, acute s.c. toxicity in [redacted] rats.

Review and Evaluation of Pharmacology and Toxicology Data [redacted] Lois M. Freed, Ph.D., 5/3/96]: no nonclinical studies were submitted [redacted]; however, previous nonclinical studies were discussed including 13-wk t.d. toxicity studies in rat and dog.

Review and Evaluation of Pharmacology and Toxicology Data [redacted] Kathleen Haberny, Ph.D., 10/19/98]: no nonclinical studies were reviewed.

[Portions of this NDA were provided electronically (scanned images).]

Executive Summary

I. Recommendations

A. Recommendation on Approvability:

From a pharmacology/toxicology standpoint, it is recommended that this NDA not be approved due to the lack of adequate assessment of carcinogenic potential. Specifically, the sponsor has not provided the data for either the mouse or rat carcinogenicity studies in a format that will allow for independent review of the results. The sponsor has committed to providing electronic datasets for the studies; however, they have not been received.

B. Recommendation for Nonclinical Studies:

Although not a basis for the nonapprovable recommendation, the sponsor needs to provide additional information regarding the genotoxic potential of selegiline STS.

The following information should be relayed to the sponsor:

Regarding the genotoxicity studies, you should conduct a repeat Ames test using concentrations of selegiline sufficient to produce cytotoxicity in each tester strain, with and without metabolic activation. You should also conduct a repeat *in vivo* cytogenetics assay unless you can provide (a) justification for the use of the oral route to support your transdermal formulation and (b) documentation that the study was conducted adequately. You have stated that the mouse lymphoma assay and the *in vitro* chromosomal aberration assay conducted by [redacted] were invalid due to serious methodological problems. The *in vivo* cytogenetics assay was also conducted by [redacted] therefore, we need additional assurance that this study was adequately conducted. If you cannot provide justification that the oral route is adequate to support the transdermal route, then a repeat assay should be conducted (using an appropriate route) and no additional validation of the *in vivo* cytogenetics assay would be necessary.

C. Recommendations on Labeling: none.

II. Summary of Nonclinical Findings

Selegiline has been demonstrated to be an MAO inhibitor, with selectivity for MAO-B following low-dose oral administration. At higher plasma exposures achieved with transdermal delivery, selegiline was shown to equally inhibit MAO-A and MAO-B in rat brain [and cardiac tissue], while maintaining some selectivity for MAO-B over MAO-A in intestine. Based on these findings, the sponsor concluded that selegiline administered transdermally would result in sufficient inhibition of MAO-A to exert an antidepressant effect while minimizing the risk of a hypertensive reaction.

The primary findings in the chronic transdermal toxicity studies conducted in rat and dog were adverse effects on body weight and local irritation. Local irritation was observed even in control animals receiving the patch; however, there was evidence in some studies of drug-related irritation. Selegiline STS had no effects on mating and fertility in rats; however, sperm concentration and total count were reduced suggesting a possible adverse effect on male fertility. In embryofetal development studies in rat and rabbit, selegiline STS was associated with adverse fetal effects, including decreases in fetal body wt (in rat), an increased incidence of visceral

malformations in both species and an increased incidence of total malformations in rat; no pattern of malformations was observed. Selegiline STS also exerted adverse effects on peri/postnatal development, resulting in reduced pup survival at birth and throughout the lactation period and delays in achieving developmental milestones. In addition, there was a decrease in litter size in the F_1 generation assessed for reproductive performance. No-effect levels were established for all but developmental delays.

The oral carcinogenicity studies conducted in mouse and rat could not be completely evaluated due to the lack of data in a format that would allow for independent evaluation. Based on the review of the data in the available format, it would appear that additional assessment is needed, at least in the mouse. However, a final decision as to the need for additional assessment of carcinogenic potential await the sponsor's submission of datasets and review of those data. Factors that must be considered in making a final determination include, in addition to the results of the statistical analysis, the adequacy of plasma drug levels achieved in the oral carcinogenicity studies relative to those in humans at the maximum clinical dose (particularly if the sponsor pursues higher clinical doses) and, possibly, the need to assess local dermal effects.

Numerous genotoxicity studies were conducted, however, they do not provide an adequate assessment of genotoxicity. The Ames test was negative, but was inadequate due to the lack of any evidence of cytotoxicity for the majority of tester strains tested. The *in vivo* micronucleus assay, also negative, needs additional data justifying the use of the oral route to support a transdermal formulation and documentation that the study was conducted using valid methodology. Selegiline produced increases in small and large colonies (indicative of clastogenic and mutagenic effects) in 2 separate mouse lymphoma assays [the sponsor considered one assay invalid]. Two *in vitro* chromosomal aberration assays in human lymphocytes were conducted; one was positive [the sponsor considered this assay invalid] and a repeat study was negative.

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY

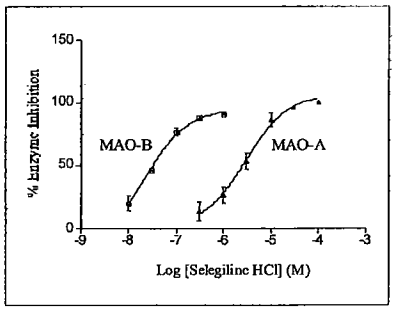
The sponsor provided an integrated summary of the pharmacology data, as well as summaries of individual study reports [Sections 5.A, 5B]. The following is based on these summaries, unless otherwise indicated.

Selegiline has been characterized as a selective, irreversible inhibitor of MAO-B (metabolizes DA, NE, and 5HT) based on the results of a variety of *in vitro* and *in vivo* assays. This activity is the basis for the use of oral selegiline in the treatment of late-stage Parkinson's disease. At higher doses, selegiline also inhibits MAO-A (selectively metabolizes DA and NE). In Parkinson's disease patients, the recommended daily dose (5 mg b.i.d.) is below the dose at which MAO-B selectivity is lost; limiting the clinical dose minimizes the risk of the "cheese reaction" associated with inhibition of intestinal MAO-A. The sponsor noted that, in contrast to Parkinson's disease, evidence suggests that MAO-A inhibition may be necessary for antidepressant activity [discussed further below]. Given orally, selegiline cannot be given at sufficiently high enough doses (in humans) to inhibit brain MAO-A without unacceptable side effects [i.e., hypertension]. Therefore, the sponsor has developed a transdermal formulation in an attempt to preferentially increase circulating (and, therefore, brain) levels of selegiline [and decrease metabolite levels] while minimizing effects on gastrointestinal MAO-A activity.

Mechanism of Action

The sponsor conducted a number of studies in order to compare the pharmacological effects of oral and transdermal selegiline. [Different formulations were used in these studies: selegiline HCl, selegiline STS, and an alternative transdermal formulation.] The following findings were obtained in a series of *in vivo*, *ex vivo*, and *in vivo* studies:

(a) using liver and brain homogenates from Sprague-Dawley rat, it was demonstrated *in vitro* that selegiline inhibited MAO-A and MAO-B activity at IC_{50}'s of 2.5 and 0.035 μM, respectively. The data are illustrated in the following sponsor's figure:



(b) in a study [report not found in Section 5B] in Sprague-Dawley rat comparing acute effects of orally and transdermally administered selegiline, transdermal selegiline (1) was 15- and 23-fold more potent in inhibiting MAO-B and MAO-A, respectively, in brain compared to oral dosing, (2) was 45-fold more potent at inhibiting MAO-B than MAO-A in brain, (3) was 12-fold more potent at inhibiting MAO-B in the GI compared to oral dosing, (4) was >67-fold more potent at inhibiting MAO-B compared to MAO-A in the GI compared to oral dosing. (5) didn't completely inhibit MAO-A in the GI at the highest dose tested [22 mg/kg] when administered transdermally. When administered orally, selegiline was 3.5-fold more potent at inhibiting MAO-B as compared to MAO-A in GI epithelium. The data were summarized in the following sponsor's table:

Table 2. ***In Vivo*** **Comparison of IC_{50} Values For MAO Inhibition in Rat Brain and Gastrointestinal Epithelium Following Transdermal Doses of Selegiline or Oral Doses of Selegiline HCl**

	IC_{50} Value (mg/kg)			
	Brain (striatum)		Gastrointestinal Epithelium	
Route	MAO-B	MAO-A	MAO-B	MAO-A
Transdermal	0.15	6.78	0.33	a
Oral	2.22	157	4.15	14.72

[a]Complete enzyme inhibition was not achieved at the highest dose evaluated (22 mg/kg)

(c) study PHARM16 was conducted in male Sprague-Dawley rat in order to assess the effects of multiple dosing [29 days] on MAO-A and MAO-B activity. Following 29 days of treatment with selegiline STS [0, 30, 120 mg/kg], various brain [striatum, hippocampus, frontal cortex], cardiac [atria, ventricles], and GI [ileum (smooth muscle, epithelial cells) regions were for assessment of MAO-A and MAO-B activity. The data were summarized in the sponsor's table below. Selegiline STS produced a non-dose-related decrease in MAO-A and MAO-B activity in brain, heart, and GI; no MAO-B selectivity was evident in either brain or heart. The degree of inhibition of both MAO isozymes was less in GI [smooth muscle and epithelial cells] than in either brain or heart. In GI tissue, MAO-B activity was inhibited to a greater extent than MAO-A.

Table 1. Effects of 30 Days STS on MAO-A and MAO-B Activities in Regions of Brain, Heart and Intestine

Tissue	Enzyme	Enzyme Activity (nmoles product formed/mg protein/hr)			
		Untreated Control	Placebo Control	30 mg/kg/day STS	120 mg/kg/day STS
Striata	MAO-A	162 ± 12.8	142 ± 3.52	8.61 ± 0.71	7.34 ± 0.49
	MAO-B	27.4 ± 1.83	32.9 ± 1.25	2.98 ± 0.11	2.68 ± 0.10
Cerebral Cortices	MAO-A	185 ± 2.86	177 ± 4.15	22.1 ± 0.54	14.7 ± 0.29
	MAO-B	90.6 ± 2.48	100 ± 2.49	10.3 ± 0.18	10.0 ± 0.33
Hippocampi	MAO-A	238 ± 3.60	214 ± 7.92	22.5 ± 1.46	17.9 ± 0.32
	MAO-B	59.6 ± 2.37	69.5 ± 2.95	7.57 ± 0.37	7.47 ± 0.14
Atria	MAO-A	205 ± 21.0	284 ± 29.7	48.1 ± 2.28	36.4 ± 2.33
	MAO-B	10.0 ± 0.78	9.90 ± 0.45	2.68 ± 0.18	2.42 ± 0.14
Ventricle	MAO-A	475 ± 57.6	674 ± 63.7	97.0 ± 9.54	94.0 ± 8.95
	MAO-B	14.5 ± 1.99	18.0 ± 1.67	3.03 ± 0.18	3.19 ± 0.28
Intestinal Smooth Muscle	MAO-A	118 ± 9.90	132 ± 7.91	64.2 ± 1.89	65.4 ± 2.78
	MAO-B	25.1 ± 2.62	33.1 ± 1.05	9.43 ± 0.58	9.90 ± 0.64
Intestinal Epithelial Cells	MAO-A	89.8 ± 3.67	80.9 ± 2.48	66.1 ± 3.04	57.0 ± 5.14
	MAO-B	55.9 ± 8.59	44.6 ± 2.09	25.0 ± 2.81	23.4 ± 3.24

Each value is the mean ± S.E.M. of tissue determinations from 4-8 animals/group. Enzyme activities in all animals receiving the STS were statistically different from untreated control group animals, $p<0.05$.

Based on these findings, the sponsor concluded that selegiline administered transdermal would result in sufficient inhibition of MAO-A (and MAO-B) to warrant development as an antidepressant, while not having an apparent risk of a "cheese reaction".

(d) study PHARM14 was conducted in male Sprague-Dawley rats and assessed the effects of multiple dosing with selegiline STS [0, 30, 120 mg/kg] for 1-mo on density and binding affinity of certain

receptors [adrenergic α_2, β_1, β_2, $5HT_2$, $5HT_{1A}$] thought to be involved in antidepressant effects of drugs or previously shown to be affected by other recognized antidepressant drugs. $5HT_{1A}$ was assayed in rat hippocampus, whereas the other receptors were assayed in rat cerebral cortex. The data were summarized in the following sponsor's table:

Table 3. Effects of the STS on Receptor Regulation in Rat Brain

Receptor	Brain Region	Parameter	Placebo Patch	Untreated Controls	STS 30 mg/kg/day	STS 120 mg/kg/day
α_2	cerebral cortex (n=9)	Bmax	86 ± 6	84 ± 5	84 ± 5	79 ± 4
		Kd	0.64 ± 0.04	0.62 ± 0.05	0.75 ± 0.07	0.66 ± 0.06
β_1	cerebral cortex (n=10)	Bmax	72 ± 3	73 ± 3	53 ± 4***	57 ± 3**
		Kd	0.22 ± 0.02.	0.23 ± 0.02	0.25 ± 0.02	0.26 ± 0.02
β_2	cerebral cortex (n=10)	Bmax	59 ± 5	58 ± 7	44 ± 3*	43 ± 5*
		Kd	1.34 ± 0.09	1.26 ± 0.09	1.14 ± 0.13	1.01 ± 0.08*
$5\text{-}HT_{1A}$	hippocampus (n=9)	Bmax	123 ± 18	149 ± 16	136 ± 14	126 ± 15
		Kd	1.87 ± 0.14	1.74 ± 0.12	1.64 ± 0.11	1.80 ± 0.16
$5\text{-}HT_2$	cerebral cortex (n=9)	Bmax	177 ± 17	195 ± 19	141 ± 9	77 ± 11***
		Kd	1.05 ± 0.22	0.95 ± 0.24	0.70 ± 0.17	0.77 ± 0.18

Each value is the mean ± S.E.M.; the number of tissues is in parentheses. Bmax values are presented in fmoles/mg protein and Kd values are nM. Significantly different from placebo control group ,*p<.05, **p<.01, ***p<.001.

Selegiline STS significantly decreased the density of β_1, β_2, and $5HT_2$ receptors and slightly increased binding affinity for the β_2 receptor, but had no effect on the α_2 or $5HT_{1A}$ receptors. [The sponsor noted that the $5HT_{1A}$ receptor seems "...to be of importance in the pathogenesis of depression and in the mode of action of antidepressant drugs" and that "Most antidepressant drugs, regardless of acute biochemical effects, result in the down-regulation of α_1 adrenergic and the $5HT_2$ and $5HT_{1A}$ serotonergic receptors in the rat central nervous system, and the time course of this effect in rats parallels the onset of antidepressant action in patients with major depressive disorder".

Drug Activity Related to Proposed Indication: the sponsor submitted only 1 study of selegiline in an *in vivo* paradigm considered reflective of antidepressant activity [Gordon *et al. Pharmacol Biochem Behav* 63:501-506, 1999]. Gordon *et al.* compared the effects of 7 daily doses of oral [0, 2, 10, 30, and 100 mg/kg by gavage] and transdermal [delivered doses: 0.4, 2.3, and 8.7 mg/kg/day] selegiline in the force-swim test in male Fischer 344 rats [5-6/grp]. MAO-A and MAO-B inhibition in brain was also assessed in this study. The oral HD was discontinued after the death of 1 of 2 rats receiving this dose. The animal died on Day 6; necropsy findings consisted of signs of self-mutilation of "...digits of both forelimbs, with loss of significant quantities of blood..." When administered orally, selegiline significantly reduced immobility time (20-30%) on Days 4-7, but had no effect on latency; both latency and immobility were affected at the HD (increased and decreased, respectively); however, as noted, this dose was excessively toxic. When administered via transdermal patch, selegiline reduced immobility time (50-80%) and increased latency (5-7 fold) at the HD. With both routes of administration, selegline produced near maximum inhibition of brain (cortex) MAO-B activity at all doses, whereas MAO-A activity was inhibited in a dose-related manner [IC_{50} = 19.8 ±1.27 mg/kg/day and 1.1 ± 2.27 mg/kg/day with oral and transdermal, respectively]. Inhibition of MAO-A was nearly complete at the HDs.

Ancillary Pharmacology Studies: the affinity of selegiline for a battery of receptors/binding sites [adrenergic, dopaminergic, serotonergic, dopamine transporter, NMDA, glutamate kainate, muscarinic, serotonin transporter, rolipram] was tested *in vitro*. Sub-micromolar affinity (K_i) was noted only for the human recombinant adrenergic α_{2B} receptor [284 nM]. No affinity [K_i >10 μM] was noted at dopamine receptors, adrenergic β_3, glutamate, muscarinic M_1-M_5, nicotinic, or rolipram receptor/sites.

Selegiline STS was tested in 3 *in vivo* studies assessing secondary CNS effects of selegiline STS. In the hexobarbital-induced sleeping time assay (100 mg/kg i.p.), selegiline STS was tested at doses of 0, 30, 60, and 120 mg/kg for 4 consecutive days in Sprague-Dawley rats. Selegiline STS did not significantly affect the occurrence of loss-of-righting response following hexobarbital, or the duration of the response at doses of 30 or 60 mg/kg. The duration of the response was significantly increased 2.3-fold in HDM on Day 5. The latency of the response was not consistently affected by selegiline STS. In males, latency was significantly reduced in LD (58%) and HD (73%) males on Day 1; latency was also reduced in HDM on Day 5 (70%), although the effect was not statistically significant. In females, latency was significantly increased in MDF on Day 1 (2.3-fold), and significantly reduced at all doses on Day 3 (36-56%; not dose-related) and at the HD on Day 5 (80%); latency was also reduced at the lower doses on Day 5 (≈70%), although the effect was not statistically significant.

The analgesic potential of selegiline STS [daily for 4 days; 0, 30, 60, 120 mg/kg] was tested in two paradigms [acetic acid-induced writhing, tail withdrawal] in male Sprague-Dawley rats. Selegiline STS had no effect in either paradigm. The positive controls, aspirin [acetic acid-induced writhing] and morphine [tail withdrawal], both exhibited significant analgesic effects.

The anticonvulsant potential of selegiline STS [4 consecutive days of dosing; 0, 30, 60, 120 mg/kg] was tested in male Sprague-Dawley rats using metrazol (85 mg/kg s.c.) and ecs to induce seizures. Phenobarbitone (30 mg/kg p.o.) was used as the positive control. Selegiline STS had no effect on seizures or deaths in animals treated with either MTZ or ecs. Phenobarbitone protected against both convulsive agents.

Pharmacology summary and conclusions: selegiline is acknowledged to be a selective irreversible MAO inhibitor [MAOI], with selectivity for MAO-B at lower doses. MAOI activity has been demonstrated *in vitro* and *in vivo* in previously conducted studies and in studies submitted by the sponsor. Given orally, however, selegiline does not appear to penetrate the brain sufficiently to inhibit MAO-A, an action the sponsor hypothesizes is necessary for selegiline to exert antidepressant activity, without producing adverse [i.e., hypertensive] effects. Therefore, a transdermal formulation has been developed. The pharmacology studies submitted by the sponsor indicate that selegiline administered transdermally (STS) inhibits MAO-A and MAO-B. When administered to male Sprague-Dawley rats for 1 month, selegiline STS exhibited MAO-A and MAO-B to a greater extent in brain and heart than in GI, but showed selectivity for MAO-B only in GI (smooth muscle, epithelial cells). These data suggest that sufficient MAO-A inhibition could be achieved to obtain antidepressant activity without unacceptable effects on intestinal MAO-A. The sponsor also cited a published report demonstrating effects of transdermal selegiline consistent with antidepressant activity in an animal model considered predictive of antidepressant efficacy [i.e., forced swim test]; the effect dose [8.7 mg/kg/day] is comparable to a 1.4 mg/kg/day dose in humans.

Selegiline STS's effects on hexobarbital-induced sleep, and analgesic and anticonvulsant potential were tested in rats following multiple dosing. Selegiline STS prolonged sleep time at 120 mg/kg [but not lower doses] following 4 consecutive doses. Neither analgesic nor anticonvulsant potential was observed following 4 days of dosing at doses up to 120 mg/kg.

II. SAFETY PHARMACOLOGY

Neurological effects

The sponsor submitted 4 studies assessing the CNS effects of selegiline STS. In study PHARM01, selegiline STS was tested in male Sprague-Dawley rat using a modified Irwin Multidimensional Observation Assessment Test. Selegiline STS was administered for 4 consecutive days at doses of 0, 30,

60, and 120 mg/kg/day. CNS effects and body temperature were assessed on Days 1 [8 hrs following placement of patch], Day 3, and Day 5. [Peak levels were considered to have been achieved by 8 hrs after start of dosing.] Notable findings include the following: (a) an increase in passivity in selegiline-treated animals [0/4 CP, 1/4 LD, 2/4 MD, 2/4 HD] on Day 1, (b) a decrease in body tone in selegiline-treated animals on Day 1 [4/4 CP, 3/4 LD, 1/4 MD, 0/4 HD], Day 3 [4/4 CP, 0/4 LD, 1/4 MD, 1/4 HD], (c) a decrease in pain response in selegiline-treated animals [4/4 CP, 3/4 LD, 3/4 MD, 2/4 HD], (d) a decrease in fearfulness only in 1/4 HD animals on Day 3, (e) decreased cutaneous blood flow only in 1/4 HD animals on Day 3. A number of findings were noted, primarily at the HD, on Day 5. The sponsor indicated that these findings (summarized in the following sponsor's table) are suggestive of "slight" CNS stimulation.

		Day 5			
Pupil Diameter	4	4/4	4/4	4/4	4/4
Touch Response*	4	3/4	4/4	2/4	2/4
Fearfulness*	4	4/4	4/4	2/4	2/4
Pinna Reflex	0	4/4	4/4	4/4	4/4
Corneal Reflex	0	4/4	4/4	4/4	4/4
Catalepsy	0	4/4	4/4	4/4	4/4
Passivity*	0	2/4	3/4	3/4	¾
Aggressiveness*	0	4/4	4/4	4/4	¾
Body Tone*	4	4/4	4/4	1/4	¼
Grip Strength	4	4/4	4/4	4/4	¼
Cutaneous Blood Flow*	4	4/4	4/4	4/4	¼
Cyanosis*	0	4/4	4/4	3/4	4/4
Ptosis	0	4/4	4/4	4/4	4/4
Lacrimation	0	4/4	4/4	4/4	4/4
Salivation	0	4/4	4/4	4/4	4/4
Pain Response*	4	2/4	3/4	3/4	2/4
Hypothermia	0	4/4	4/4	4/4	4/4
Paralysis	0	4/4	4/4	4/4	4/4
Grooming	4	4/4	4/4	4/4	4/4
Diarrhea	0	4/4	4/4	4/4	4/4
Vocalization*	0	4/4	4/4	3/4	2/4
Increased Urination	0	4/4	4/4	4/4	4/4

Animals receiving the STS (or placebo patch) were evaluated at the following times during the study: Day 1 (8 hours after initiation of dosing); Day 3 (48 hours after initiation of dosing and prior to removal of the second dose); and Day 5 (96 hours after initiation of dosing and prior to removal of the fourth dose).
* These behaviors were altered in some animals in the placebo patch control or STS-treated groups.

There were no apparent drug-related effects on body temperature.

The effects of selegiline STS on spontaneous motor activity [SMA; study PHARM05] and rotarod performance were tested at doses of 0, 30, 60, and 120 mg/kg; patches were applied daily for 4 days. Testing times were the same as those used for the Irwin screen. SMA was significantly increased in male Sprague-Dawley rats at the MD [51-83%] and HD [84-150%] on Days 3 and 5; the positive control, d-amphetamine [10 mg/kg p.o.], increased SMA on all days [210-260%]. Rotarod performance [study PHARM12] was slight (but significantly) improved in female Sprague-Dawley at the HD [40-45% increase in maximum performance time] on Days 1-2, and the MD [58%] and HD [37%] on Day 5. Selegiline STS had no proconvulsant effect on metrazol- [40 mg/kg s.c.] or ecs-induced convulsions in male Sprague-Dawley rats at doses of 0, 30, 60, and 120 mg/kg [study PHARM17].

Cardiovascular effects: selegiline HCl was tested *in vitro* in a sheep Purkinje fiber preparation in order to assess the potential for prolongation of the QT interval [study PHARM04]. "Ten Purkinje fibers from 10 separate hearts were used for study." According to the report, fibers were continually stimulated "...at 1 second intervals using 1 ms wide isolated constant current pulses having an amplitude equal to twice the diastolic (resting) threshold value. A relatively high stimulus strength was used to ensure that all the nerves within the bundle were stimulated". Each fiber was treated with vehicle, followed by selegiline at 3 (increasing) concentrations [10^{-8}, 10^{-7}, 10^{-6} M], and 4-aminopyridine [10^{-6} M, positive control]. [It was expected that 4-AP would produced increases in APD_{50} and APD_{90}.] Fibers were exposed to each treatment for 30 min. [The sponsor noted that the HC of selegiline was equivalent to a circulating level

of ≈187 µg/mL.] The following parameters were recorded: upstroke amplitude [AMP], resting membrane potential [RMP], V_{max} [maximum rate of depolarization], APD_{50}, and APD_{90}. Baseline parameter values were as follows: APD_{50} = 109.5 ± 36.5 msec, APD_{90} = 177.7 ± 33.5 msec, V_{max} = 543.5 ± 91.3 V/sec, AMP = 117.8 ± 4.27 mV, RMP = -87.3 ± 2.28 mV. Selegiline had no significant effect [all changes at the HC were <10%] on any parameter assessed. 4-AP significantly increased both APD_{50} [86%] and APD_{90} [54%].

Gastrointestinal effects: the sponsor conducted a study in isolated guinea pig [Dunkin-Hartley; n = 9] ileum [study PHARM11]. Selegiline was tested at concentrations of 10^{-8} to 10^{-6} M. Selegiline's effect on basal tone was tested as well as it's effect on ACh, histamine, 5HT, and $BaCl_2$-induced contractions. Selegiline had no effect on basal tone, but did inhibit 5HT-induced contractions at all concentrations [significant at 10^{-7} and 10^{-6} M] in a concentration-related manner [14.2 ± 12.11, -3.2 ± 13.76, -13.3 ± 13.44, and -14.8 ± 6.42% (of contraction amplitude from baseline) for C, 10^{-8}, 10^{-7}, and 10^{-6} M, respectively]. Selegiline also inhibited $BaCl_2$-induced contractions in a concentration-related manner at the two highest concentrations; however, the effect was not statistically significant.

The effect of selegiline STS on GI transit time [study PHARM10] was assessed in male Sprague-Dawley rats at dose of 0, 30, 60, and 120 mg/kg; patches were applied daily for 4 days. GI transit was assessed on Day 1 [8 hrs post application], Day 3, and Day 5. GI transit time was assessed 30 min following gavage dosing of a charcoal suspension [5% in water, 1.0 mL/rat]; the distance from the pyloric area to the "leading edge of the bolus' was used to calculate transit time [distance to leading edge of bolus*100/total length of GI tract]. Morphine [30 mg/kg p.o.] was used as a positive control. The only effect noted was an increase in distance traveled [33-38%] and % transit [i.e., a decrease in transit time] at the MD and HD on Day 1. Morphine significantly delayed [or increased transit time, i.e., decreased charcoal distance and % transit] on all days tested.

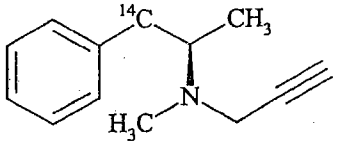
Renal effects: the effects of selegiline STS on renal parameters [urine volume, electrolyte and protein levels] were tested in male Sprague-Dawley rats at doses of 0, 30, 60, and 120 mg/kg; patches were applied daily for 4 days. Parameters were assessed on Day 1 [1-24 hrs], Day 3 [1-24 hrs], and Day 5 [1-24 hrs]. Electrolyte [Na, K, Cl] and total protein concentrations were calculated based on data from the 0-5 hr cumulative urine collections ["or a 10 mL aliquot, whichever was the least"]. There were no significant drug-related effects on the parameters assessed. However, the following were of note: (a) a decrease in urine volume at the HD on Day 3 [36% based on 24-hr collection], (b) decreases in Na, K, and Cl concentrations [mEq/mL] at the HD on Day 3 [≈60%].

Abuse liability: the assessment of abuse liability was consulted to HFD-009.

Safety pharmacology summary and conclusions: the sponsor assessed the CNS, cardiovascular, renal, and GI effects of selegiline STS (4 daily doses). The results of the CNS studies indicated a stimulatory effect of selegiline STS. However, no proconvulsant potential was observed. No significant effects were observed on cardiovascular parameters assessed *in vitro* [sheep Purkinje fibers], on GI transit time [in mice], or on renal parameters [in rats]. In an *in vitro* study, selegiline inhibited 5HT-induced contractions in isolated guinea pig ileum, but had no significant effect on ACh, histamine, or $BaCl_2$-induced contractions. Selegiline STS is expected to have little or no abuse potential [cf. Memorandum, Katherine Bonson, Ph.D., Controlled Substance Staff, HFD-009, 1/18/02].

III. PHARMACOKINETICS/TOXICOKINETICS

The PK/ADME of selegiline was tested primarily in rat, dog, rabbit, and human. In the technical summary, the sponsor stated that "...all the pivotal pharmacokinetic and toxicokinetic studies used the 20 mg selegiline/20 cm^2 patch that is intended for marketing", although some PK studies were conducted on other td formulations. Studies were conducted by [redacted]. Plasma and drug formulation analyses were generally conducted by [redacted] (sponsor) [LLOQ for all analyzed compounds = [redacted] ng/mL]. For studies using ^{14}C-selegiline, the location of the radiolabel was illustrated in the following sponsor's figure:



.HCl

PK parameters, Absorption, Distribution, Elimination

Rat. In Study APK-40-98B, selegiline was administered to male Sprague-Dawley rats (6/grp) at doses of 15.84 mg/kg i.v. (continuous 24-hr infusion) and 60 mg/kg t.d. Actual delivered doses were estimated to be 13.10 ± 0.135 mg/kg i.v. and 9.84 ± 1.294 mg/kg t.d. Serial blood samples were collected at 0.5-24 hrs after the beginning of dosing, and at 0.33-24 hrs following termination of dosing. Blood transfusions were delivered after "...every second or third blood collection interval..." One rat died in each group during transfusion; blood samples from these animals were not analyzed. In addition, data from one STS animal was not analyzed due to the following: (a) drug concentrations of selegiline "...did not decay over the 24 hrs after the patches were removed. Only 60% of the patches were still adhering to [the animal] at the end of the 24-hour dosing interval, and (b) plasma selegiline levels were "unusually high" in this animal. The data were summarized in the following sponsor's table:

Table 1. **Mean ± SD (N=5) Estimates of Pharmacokinetic Parameters for Selegiline and its Metabolites in Rats after Single 24-Hour Intravenous Infusion of Selegiline HCl (15.84 mg/kg) or Selegiline Transdermal System (60 mg/kg) Dose**

Pharmacokinetic Parameter	Selegiline		N-Desmethylselegiline		Methamphetamine		Amphetamine	
	IV	STS[a]	IV	STS	IV	STS	IV	STS
AUC(0-24) ng.hr/mL	739 ±92.7	320 ±90.9	187 ±29.5	115 ±26.5	166 ±46.4	77.3 ±19.99	143 ±45.6	62.4 ±19.99
AUC(0-∞) ng.hr/mL	818 ±87.9	376 ±118.9	205 ±29.4	130 ±29.0	194 ±53.5	91.8 ±24.10	181 ±57.6	81.6 ±25.74
AUC(0-∞) ng.hr/mL per mg/kg dosed	62.4 ±6.46	36.2[b] ±8.77	15.6 ±2.25	12.2[b] ±1.99	14.8 ±4.21	8.60[b] ±1.796	13.8 ±4.49	7.60[b] ±1.899
		39.1[c] ±9.27		13.2[c] ±2.09		9.27[c] ±1.899		8.19[c] ±2.011
Cmax ng/mL	37.7 ±4.68	20.1 ±6.10	10.4 ±1.66	6.63 ±1.762	8.61 ±2.135	3.89 ±1.007	7.80 ±2.422	3.48 ±1.152
Tmax hr	15.6 ±8.05	11.0 ±9.59	4.40 ±0.894	5.20 ±1.095	14.4 ±6.84	8.00 ±3.742	18.0 ±6.00	15.8 ±5.76
Kel hr^{-1}	0.139 ±0.0291	0.245 ±0.1471	0.297 ±0.1176	0.355 ±0.0375	0.191 ±0.0222	0.262 ±0.0497	0.163 ±0.0252	0.177 ±0.0376
t½[d] hr	4.98	2.83	2.33	1.96	3.63	2.65	4.26	3.91
Bioavailability %		56.8[b]		76.5[b,e]		57.2[b,e]		54.2[b,e]
		61.3[c]		82.5[c,e]		61.7[c,e]		58.5[c,e]
Clearance mL/min/kg	269 ±26.0							
Vss L/kg	44.8 ±10.67							

[a] N=4

[b] calculated from the difference between the assayed amount in unused reference patches and the amount remaining in patches at the end of the 24-hour application

[c] calculated from the difference between the label content of 20 mg per patch and the amount remaining in patches at the end of the 24-hour application

[d] harmonic mean (ln2/mean Kel)

[e] fraction absorbed

The PK profile of selegiline, and metabolites, desmethylselegiline, methamphetamine, and amphetamine following STS were illustrated in the following sponsor's Figure 3:

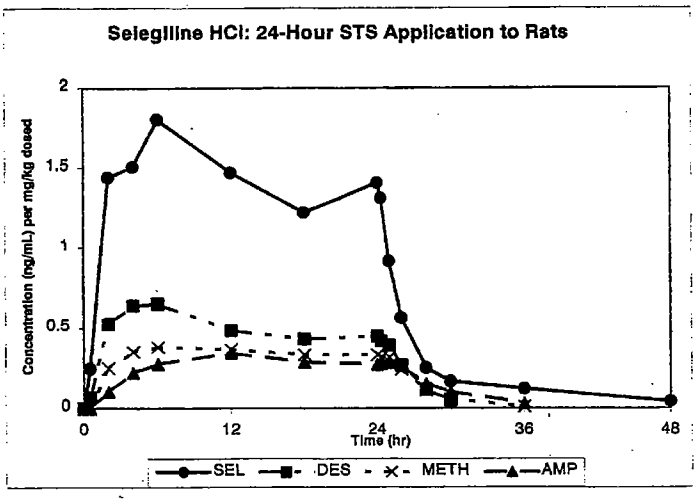


Figure 3: Mean plasma concentrations of selegiline, N-desmethylselegiline, methamphetamine, and amphetamine during and following a 24-hour application of the Selegiline Transdermal System, 60 mg/kg, to 5 male Sprague-Dawley rats (selegiline concentrations from 4 rats). Concentrations are expressed per mg/kg of delivered dose based upon 20mg selegiline per patch (Cartesian co-ordinates).

In Study APK-50-98B, selegiline was administered to Sprague-Dawley rats (48/sex; 6/sex/time point) at a dose of 120 mg/kg [the HD used in the 6-mo toxicity study] for one 24-hr period. The actual dose administered was estimated to be 24-25 mg/kg "...calculated from the theoretical content of 20 mg selegiline/patch". Blood samples were collected prior to dosing, at 0.5-24 hrs after patch application, and at 0.33-24 hrs following patch removal. Two blood samples were collected from each rat. The data were summarized in the following sponsor's table:

Table 2. Composite (N=6/Time Point) Estimates of Pharmacokinetic Parameters for Selegiline and its Metabolites in Rats after a Single Dermal Application of 120 mg/kg Selegiline via the Selegiline Transdermal System

Pharmacokinetic Parameter	Selegiline			N-Desmethylselegiline			Methamphetamine			Amphetamine		
	Male	Female	Ratio F/M	Male	Female	Ratio F/M	Male	Female	Ratio F/M	Male	Female	Ratio F/M
AUC(0-24) ng.hr/mL	2148	1941	0.90	421	438	1.04	357	757	2.12	339	356	1.05
AUC(0-∞) ng.hr/mL	2248	2020	0.90	461	468	1.02	408	869	2.13	397	440	1.11
AUC(0-∞) ng.hr/mL per mg/kg dosed [a]	80.8	71.7	0.89	16.6	16.6	1.00	14.7	30.9	2.10	14.3	15.6	1.09
AUC(0-∞) ng.hr/mL per mg/kg dosed [b]	90.9	82.9	0.91	18.6	19.2	1.03	16.5	35.7	2.16	16.1	18.0	1.12
Cmax ng/mL	117	114	0.97	23.2	26.1	1.13	19.7	48.8	2.48	17.3	20.8	1.20
Tmax hr	6.00	12.00	2.0	2.00	12.00	6.0	2.00	12.00	6.0	6.00	12.00	2.0
Kel hr^{-1}	0.5987	0.5058	0.84	0.6395	0.5374	0.84	0.1916	0.2857	1.49	0.1850	0.2734	1.48
t½ hr	1.16	1.37	1.18	1.08	1.29	1.19	3.62	2.43	0.67	3.75	2.54	0.68

[a] calculated from the difference between the assayed amount in unused reference patches and the amount remaining in patches at the end of the 24-hour application

[b] calculated from the difference between the label content of 20 mg per patch and the amount remaining in patches at the end of the 24-hour application

The primary difference between males and females was the plasma levels of methamphetamine, which were ≈2-fold higher in females (based on AUC).

[Study APK-01-92L involved the administration of selegiline as acute i.v. [15 mg/kg] and dermal (32 mg transdermal patch) doses to male Sprague-Dawley rats. Since a different (earlier) transdermal formulation was used in this study, the report was not reviewed.]

In Study APK-43-98B, ^{14}C-selegiline was administered dermally to male Sprague-Dawley rats at doses of 48 mg/kg as a solution (vehicle: DMSO; Grps 1 and 2) or non-radiolabeled selegiline as a patch (STS; Grp 2). Grp 1 received a single dose of ^{14}C-selegiline over one 24-hr period; Grp 2 received selegiline-STS daily for 6 days [patches replaced every 24 hrs], followed by a single dose of ^{14}C-selegiline solution (dermally applied) for one 24-hr period on Day 7. Blood samples were collected as follows: Grp 1: at 2-168 hrs following dosing (3/time point), Grp 2: at 23-24 hrs post dosing on Day 1 (i.e., immediately prior to patch replacement) and at 2-hr postdosing on Day 6, and at 2 and 168 hrs post dosing on Day 7. Urine samples were collected over 24-hr periods on Days 1, 2, and 6 of STS treatment from Grp 2 animals scheduled for 2-hr postdosing sacrifice. In Grps 1 and 2 animals, urine samples were collected at various intervals from 0-168 hrs postdosing with ^{14}C-selegiline. Fecal samples were collected according to the same schedule as for urine samples. Tissue samples were collected at 2-168 hrs postdosing.

Following single and multiple dosing, peak plasma levels of radioactivity were achieved at 2 hrs postdosing, with plasma radioactivity declining over the 48-hr period postdosing. Radioactivity was fairly widely distributed among tissues after single and multiple dosing, with peak levels occurring at 2-8 hrs postdosing. Two hrs following an acute dose, highest levels of radioactivity were detected in GI, "...liver, kidney, lacrimal gland, salivary glands, abdominal fat, and urinary bladder." At 168 hrs postdosing, radioactivity was detectable in most tissue examined, however, at markedly lower levels (i.e.,

0.01-8% of peak). Tissue radioactivity data at 2, 8, and 24 hrs postdosing were summarized in the following sponsor's table:

Table 4

Mean Concentrations of Radioactivity in Tissues Following a Single Dermal Dose of [^{14}C]-Selegiline HCl (μgEq/g)*

Tissue Type	2 Hours Post Dose			
	Group I		Group II	
	Mean	Standard Deviation	Mean	Standard Deviation
Adrenals	4.315	0.951	4.805	1.949
Aorta	3.405	0.649	4.132	3.338
Bone	0.561	0.063	0.644	0.122
Bone Marrow	2.745	0.264	3.087	0.483
Brain	2.031	0.091	2.319	0.719
Eye (lens only)	0.482	0.042	0.788	0.318
Eye (without lens)	2.008	0.315	2.579	0.895
Fat (abdominal)	6.059	1.529	7.062	2.752
Heart	1.298	0.168	1.305	0.452
Kidneys	17.461	8.078	12.680	4.411
Lacrimal Glands	16.840	4.595	16.594	1.879
Large Intestine	3.985	0.709	3.011	1.353
Liver	24.486	2.660	21.629	2.995
Lungs	3.816	0.668	4.592	1.877
Lymph Nodes	3.798	NC	5.367	0.744
Muscle	1.157	0.029	1.426	0.256

(n = 3 animals per group)
NC=Not Calculated, (n=2)
*Concentration based on specific activity of Selegiline HCl dosing solution. Ratio of Selegiline free base to HCl salt is [redacted]

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Tissue Type	2 Hours Post Dose			
	Group I		Group II	
	Mean	Standard Deviation	Mean	Standard Deviation
Pancreas	3.776	0.106	5.987	1.871
Pituitary	2.391	0.520	3.190	0.789
Prostate	3.681	0.682	3.533	0.877
Salivary Glands	6.422	1.036	8.424	2.077
Skin (non-dose site)	4.138	1.175	3.298	NC
Small Intestine	24.851	6.457	20.866	7.242
Spinal Cord	2.057	0.157	2.051	0.433
Spleen	4.046	0.202	4.735	1.427
Stomach	8.632	3.041	5.198	0.708
Testes	2.138	0.313	1.931	0.336
Thymus	2.306	0.154	2.913	0.900
Thyroid	2.445	0.355	3.519	2.369
Urinary Bladder	5.165	1.579	18.400	6.203
Vena Cava	5.058	1.327	4.784	2.712
Plasma	1.379	0.165	1.310	0.541
Whole Blood	1.538	0.158	1.811	0.606

Tissue Type	Group I			
	8 Hours		24 Hours	
	Mean	Standard Deviation	Mean	Standard Deviation
Adrenals	2.705	0.249	0.832	0.052
Aorta	2.105	0.279	0.611	0.099
Bone	0.380	0.078	0.196	0.256
Bone Marrow	1.697	NC	0.395	0.089
Brain	1.395	0.420	0.316	0.029
Eye (lens only)	0.440	0.122	0.101	0.009
Eye (without lens)	1.324	0.205	0.406	0.005
Fat (abdominal)	9.500	0.463	2.930	1.319
Heart	0.839	0.107	0.352	0.083
Kidneys	16.528	2.019	5.599	2.084
Lacrimal Glands	21.391	3.917	5.121	1.701
Large Intestine	12.024	4.756	3.657	1.211
Liver	37.338	0.301	14.856	0.991
Lungs	2.861	0.768	0.765	0.098
Lymph Nodes	3.014	1.246	0.570	0.103
Muscle	0.892	0.097	0.210	0.017

Tissue Type	Group I			
	8 Hours		24 Hours	
	Mean	Standard Deviation	Mean	Standard Deviation
Pancreas	2.733	0.509	0.689	0.103
Pituitary	2.587	0.886	0.640	0.025
Prostate	3.607	1.595	0.642	0.137
Salivary Glands	4.415	0.661	1.238	0.284
Skin (non-dose site)	3.006	0.535	3.031	3.148
Small Intestine	26.252	4.252	7.079	0.849
Spinal Cord	1.362	0.303	0.277	0.035
Spleen	2.565	0.867	0.427	0.034
Stomach	2.612	1.002	0.519	0.138
Testes	1.515	0.408	0.323	0.031
Thymus	1.538	0.283	0.327	0.002
Thyroid	2.140	1.047	0.591	0.137
Urinary Bladder	9.968	4.602	3.545	0.906
Vena Cava	2.988	0.500	0.966	0.331
Plasma	1.245	0.141	0.457	0.047
Whole Blood	1.336	0.195	0.467	0.033

Tissue levels of radioactivity exceeded plasma levels in all tissues examined except for bone, eye (lens), heart, muscle,

Analysis of application site indicated that 0.8-0.74% of the applied dose remained at the site at 168 hrs postdosing. The sponsor estimated that 32% of the administered dose was absorbed. [At 168 hrs postdosing, 50-43% of dose radioactivity was recovered in wrappings, 32% in excreta, 3-6% in cage wash, and 0.33-0.28% in carcasses. Total recovery of radioactivity was 83-77%.]

The major route of elimination was via the urine, with urinary radioactivity accounting for 24-27% of administered dose. Fecal radioactivity accounted for only 2% of administered dose.

Tissue distribution in pigmented rats was assessed in Study APK-57-98B. ^{14}C-selegiline was administered as a single dermal dose (in DMSO, 48 mg/kg; 2/sex/strain) or as unlabeled selegiline for 6 days (1/sex/strain) using the STS (60 mg/kg) followed by a single dermal dose of ^{14}C-selegiline (in DMSO, 48 mg/kg) in Sprague-Dawley or Long-Evans rats (4/strain). The sponsor noted that the radiolabeled dose was selected to estimate the amount absorbed transdermally using the STS (i.e., 38% of the 60 mg/kg dose over 24 hrs). One animal/sex/strain/time point was sacrificed at 2 or 48 hrs postdosing; the remaining animals were sacrificed 2 hrs after application of the dose of ^{14}C-selegiline. Tissue radioactivity was assessed using whole body autoradiography. Tissue radioactivity was assessed qualitatively using a bioimaging analyzer . [Results are based on the sponsor's interpretation of the images.]

In Sprague-Dawley rats, highest tissue levels of radioactivity were detected in preputial gland, urinary bladder, and small intestine (contents), and at the administration site. Moderate levels were detected in "...the Harderian gland, salivary glands, lacrimal glands, liver, kidney, stomach contents and nasal mucosa". At 48 hrs postdosing, "high" levels were still detected in preputial gland and at the administration site, and "moderate" levels were still detected in liver, kidney, GI, lacrimal gland, and nasal mucosa. Tissue distribution was similar in Long-Evans rats, except for an increased level of

radioactivity in the choroid-retina, indicating binding in the pigmented eye; little or no radioactivity was detected in pigmented skin. Tissue distribution was similar following single and multiple dosing.

In Study APK-45-98B, biliary excretion of ^{14}C-selegiline was assessed in 3 bile-cannulated male Sprague-Dawley rats following a single dermal dose (solution in DMSO) of 48 mg/kg. Urine samples were collected at varying intervals from 0 to 48 hrs postdosing. Bile samples were to have been collected during the same intervals; however, due to problems with bile flow, samples were collected from 2 animals and only at 0-2 hrs postdosing for one animals and at 24-48 hrs postdosing for the 2nd animal. Only 1 of the 3 animals produced feces throughout the study period; therefore, samples were collected according to schedule (as for urine) only in the 1 animal. Feces were collected for a 2nd animal at 0-2 hrs postdosing, and no feces were available for the 3rd animal. Complete data were available for only 1 animal. In this animal, ' % of dose radioactivity was recovered in urine, bile, and feces, respectively. Total recovery of dose radioactivity was .

Dogs. comparisons of i.v. and dermal application were conducted in two studies [APK-41-98B, APK-02-921]. In Study APK-41-98B, selegiline was administered i.v.(2.54 mg/kg; 24-hr continuous infusion) and dermally [24 mg/kg (delivered dose: 2.88 mg/kg; STS) to 6 male Beagle dogs; acute doses were separated by a 3-day washout period. Blood samples were collected prior to dosing, at 0.75-24 hrs after start of dosing, and at 0.25-72 hrs following termination of dosing. The data were summarized in the sponsor's table below. For selegiline, desmethylselegiline, and methamphetamine, the $t_{1/2}$ after t.d. dosing was longer than after i.v. dosing; the sponsor attributed this to the higher levels of these compounds, allowing them to be quantitated over a longer period following t.d. dosing. The t.d. bioavailability was estimated to be ≈62%.

Table 1. Mean ± SD (N=6) Estimates of Pharmacokinetic Parameters for Selegiline and its Metabolites in Dogs after Single 24-Hour Intravenous Infusion of Selegiline HCl (3.12 mg/kg) or Selegiline Transdermal System (24 mg/kg) Dose

Pharmacokinetic Parameter	Selegiline		N-Desmethylselegiline		Methamphetamine		Amphetamine	
	IV	STS	IV	STS	IV	STS	IV	STS
AUC(0-24) ng.hr/mL	341 ±49.2	198 ±99.8	93.0 ±24.04	58.3 ±9.59	220 ±52.5	144 ±12.6	839 ±68.7	507 ±117.2
AUC(0-∞) ng.hr/mL	376 ±63.7	287 ±151.7	103 ±26.0	87.9 ±13.73	264 ±64.1	234 ±24.7	1370 ±134	1146 ±144
AUC(0-∞) ng.hr/mL per mg/kg dosed	148 ±24.4	80.4 [a] ±35.96	40.4 ±10.20	25.4 [a] ±3.79	104 ±24.7	68.2 [a] ±11.46	538 ±53.5	330 [a] ±21.7
		97.0 [b] ±43.40		30.6 [b] ±4.76		82.4 [b] ±14.4		398 [b] ±26.8
Cmax ng/mL	17.6 ±2.41	16.1 ±10.91	4.53 ±1.200	4.15 ±0.661	11.5 ±2.49	10.2 ±1.47	55.2 ±6.09	44.2 ±4.39
Tmax hr	21.5 ±4.68	22.2 ±5.00	11.7 ±5.85	22.2 ±5.00	19.8 ±6.08	21.1 ±5.15	20.5 ±6.59	25.9 ±1.20
Kel hr^{-1}	0.173 ±0.0940	0.105 ±0.0524	0.226 ±0.0751	0.109 ±0.0507	0.150 ±0.0734	0.0786 ±0.03088	0.0578 ±0.00772	0.0609 ±0.01538
t½ [c] hr	4.01	6.60	3.07	6.36	4.62	8.82	12.0	11.4
Bioavailability %		51.8 [a] ±17.28		63.9 [a,d] ±17.16		65.6 [a,d] ±10.96		60.3 [a,d] ±9.38
		62.5 [b] ±20.71		77.1 [b,d] ±20.58		79.1 [b,d] ±13.03		72.7 [b,d] ±11.14
Clearance mL/min/kg	116 ±18.6							
Vss L/kg	18.1 ±4.35							

[a] calculated from the difference between the assayed amount in unused reference patches and the amount remaining in patches at the end of the 24-hour application

[b] calculated from the difference between the label content of 20 mg per patch and the amount remaining in patches at the end of the 24-hour application

[c] harmonic mean (ln2/mean Kel)

[d] fraction absorbed

The PK of selegiline administered as an i.v. bolus [30-sec] and a transdermal patch were assessed in in Study APK-02-921. However, this study was not reviewed since the transdermal formulation was, according to the sponsor, "substantially different from the current.....Transdermal System...".

The PK of selegiline and metabolites following acute and multiple dosing was assessed in two studies [APK-51-98B, APK-44-98B]. In Study APK-51-98B, selegiline (6 or 24 mg/kg) was administered dermally (STS) to two grps of male Beagle dogs (6/grp). [The doses were the LD and HD in the 9-mo toxicity study in dog.] In each grp, animals received an acute dose, followed ≈3-wks later by the same dose level for 7 consecutive days. Blood samples were collected as follows: (a) for acute dose, samples were collected prior to dosing, at 0.75-24 hrs post application, and at 0.25-72 hrs after patch removal. (b) for multiple-dosing, samples were collected prior to dosing and at 0.75-23 hrs after patch application on Day 1 and 7 (no pre-dosing sample collected on Day 7) and at 23 hrs after patch application on Days 2-6. Based on analysis of removed patches, the actual doses delivered were 0.68 ± 0.08 and 2.91 ± 0.56 mg/kg for the acute dosing phase and 0.86 ± 0.22 and 3.27 ± 0.51 mg/kg/day during the multiple-dose phase. During the multiple-dose phase, the % of applied patches found adhering to the animal after 24 hrs ranged from 8% [on Days 4 and 7 in 1 animal] to 100% [except for the 8% reported in the 1 animal, the range was 36-100%]. In 9 of the 12 animals, the % of applied patches adhering to the animal ranged from 80-100%.

The data were summarized in the following sponsor's tables and figures:

Table 4: Pharmacokinetics of Selegiline and Metabolites After Single Applications of The Selegiline Transdermal Patch To Beagle Dogs.

Mean ± Standard Deviation (n=6) (% Coefficient of Variation)

Pharmacokinetic Parameter	Selegiline			N-Desmethylselegiline			Methamphetamine			Amphetamine		
	6 mg/kg	24 mg/kg	Ratio[a]	6 mg/kg	24 mg/kg	Ratio[a]	6 mg/kg	24 mg/kg	Ratio[a]	6 mg/kg	24 mg/kg	Ratio[a]
AUC(0-23) ng. hr/mL	46.2 ±14.10 (31%)	195 ±98.9 (51%)	4.2	14.6 ± 6.73 (46%)	36.2 ± 9.35 (26%)	2.5	27.5 ±10.59 (38%)	77.1 ±19.63 (26%)	2.8	91.3 ±33.07 (36%)	316 ± 115.7 (37%)	3.5
AUC(0-∞) ng. hr/mL	71.3 ±19.74 (28%)	352 ±139.5 (40%)	4.9	21.5 ±7.66 (36%)	67.8 ±14.74 (22%)	3.2	44.1 ±14.64 (33%)	165 ±39.8 (24%)	3.7	258 ±58.8 (23%)	1029 ±291 (28%)	4.0
AUC(0-∞) ng. hr/mL /mg/kg dosed[b]	93.6 ±25.91 (28%)	110 ±34.2 (31%)	1.2	27.7 ±8.15 (29%)	22.0 ±5.71 (26%)	0.8	57.8 ±18.79 (33%)	52.5 ±10.11 (19%)	0.9	341 ±91.5 (27%)	326 ±68.9 (21%)	1.0
AUC(0-∞) ng. hr/mL /mg/kg dosed[c]	105 ±29.2 (28%)	120 ±37.5 (31%)	1.1	31.0 ±8.94 (29%)	24.1 ±6.84 (28%)	0.8	64.7 ±21.16 (33%)	57.5 ±12.70 (22%)	0.9	382 ±105.6 (28%)	355 ±72.9 (21%)	0.9
Cmax ng/mL	4.09 ±1.146 (28%)	20.0 ±11.18 (56%)	4.9	1.32 ±0.249 (19%)	3.40 ±0.705 (21%)	2.6	2.40 ±0.795 (33%)	7.28 ±1.823 (25%)	3.0	11.0 ±3.42 (31%)	39.5 ±12.68 (32%)	3.6
Tmax hr	24.0 ±0.50 (2.1%)	24.3 ±0.10 (0.4%)	1.0	21.6 ±4.74 (22%)	24.3 ±0.13 (0.5%)	1.1	23.9 ±0.70 (2.9%)	24.5 ±0.27 (1.1%)	1.0	26.2 ±1.60 (6.1%)	27.0 ±2.68 (9.9%)	1.0
Kel hr^{-1}	0.157 ±0.0809 (52%)	0.0551 ±0.01950 (35%)	0.4	0.213 ±0.0886 (42%)	0.110 ±0.0731 (66%)	0.5	0.165 ±0.0353 (21%)	0.0598 ±0.01595 (27%)	0.4	0.0721 ±0.02181 (30%)	0.0460 ±0.00891 (19%)	0.6
t½[d] hr	4.42	12.59	2.8	3.25	6.29	1.9	4.20	11.58	2.8	9.61	15.07	1.6

[a] 24 mg/kg result divided by 6 mg/kg result
[b] calculated from assayed amount in reference patches
[c] calculated from 20mg applied in each patch
[d] harmonic mean

Table 5: Pharmacokinetics of Selegiline and Metabolites After Multiple Dosing of The Selegiline Transdermal Patch To Beagle Dogs. Mean ± Standard Deviation (n=6) (% Coefficient of Variation)

Pharmacokinetic Parameter	Selegiline			N-Desmethylselegiline			Methamphetamine			Amphetamine		
	6 mg/kg /day	24 mg/kg /day	Ratio[a]	6 mg/kg /day	24 mg/kg /day	Ratio[a]	6 mg/kg /day	24 mg/kg /day	Ratio[a]	6 mg/kg /day	24 mg/kg /day	Ratio[a]
Day 1 AUC(0-23) ng. hr/mL	54.5 ± 9.32 (17%)	253 ±111.5 (44%)	4.6	15.6 ±4.92 (32%)	46.5 ± 9.71 (20.9%)	3.0	32.3 ±7.56 (23%)	110 ±39.3 (36%)	3.4	107 ±23.4 (22%)	429 ±154.3 (36%)	4.0
AUCss ng.hr/mL	104 ±36.6 (35%)	587 ±132.8 (23%)	5.6	30.9 ±12.86 (42%)	85.7 ±8.55 (10%)	2.8	73.1 ±26.88 (37%)	309 ±115.8 (37%)	4.2	368 ±177.6 (48%)	1715 ±414 (24%)	4.7
AUCss ng.hr/mL /mg/kg dosed[c]	124 ±44.6 (36%)	146 ±15.1 (10%)	1.2	35.1 ±12.01 (34%)	21.8 ±4.42 (20%)	0.6	84.3 ±26.84 (32%)	77.8 ±30.78 (40%)	0.9	422 ±181.2 (43%)	427 ±82.7 (19%)	1.0
AUCss ng.hr/mL /mg/kg dosed[d]	126 ±45.6 (36%)	178 ±14.3 (8%)	1.4	35.8 ±12.20 (34%)	26.8 ±5.81 (22%)	0.7	85.8 ±27.29 (32%)	95.4 ±37.04 (39%)	1.1	429 ±184.1 (43%)	524 ±96.3 (18%)	1.2
Cmax,ss ng/mL	6.13 ±2.104 (34%)	30.5 ±6.08 (20%)	5.0	1.67 ±0.506 (30%)	4.21 ±0.550 (13%)	2.5	3.96 ±1.234 (31%)	14.6 ±4.97 (34%)	3.7	18.9 ±7.48 (40%)	85.1 ±18.20 (21%)	4.5
Tmax,ss Hr	12.6 ±11.41 (90%)	5.96 ±8.445 (142%)	0.5	16.5 ±7.45 (45%)	11.5 ±6.63 (58%)	0.7	12.8 ±11.16 (87%)	9.46 ±10.562 (112%)	0.7	7.13 ±4.289 (60%)	7.00 ±4.147 (59%)	1.0
Kel hr^{-1}	0.220 ±0.1102 (50%)	0.0796 ±0.01265 (16%)	0.4	0.225[b] ±0.1356 (60%)	0.107 ±0.0247 (23%)	0.5	0.200 ±0.0739 (37%)	0.0909 ±0.01458 (16%)	0.5	0.0796 ±0.02943 (37%)	0.0493 ± 0.00375 (8%)	0.6
t½[e] hr	3.15	8.71	2.8	3.08	6.50	2.1	3.47	7.63	2.2	8.70	14.06	1.6
Fluctuation (%)	77.9 ±35.66 (46%)	42.9 ±9.22 (22%)	0.6	69.2 ±34.17 (49%)	39.0 ±13.73 (35%)	0.6	64.8 ±30.29 (47%)	25.2 ±5.82 (23%)	0.4	62.2 ±22.33 (36%)	44.1 ±9.48 (22%)	0.7

[a] 24 mg/kg result divided by 6 mg/kg result
[b] n=5
[c] calculated from assayed amount in reference patches
[d] calculated from 20mg applied in each patch
[e] harmonic mean

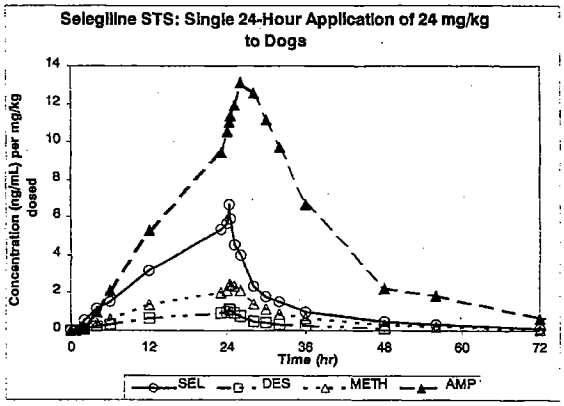

Figure 3: Mean concentrations of selegiline and metabolites after a single 24-hour application of the Selegiline Transdermal System 24 mg/kg. Concentrations are expressed per mg/kg of delivered dose based upon 20mg selegiline per patch (Cartesian co-ordinates).

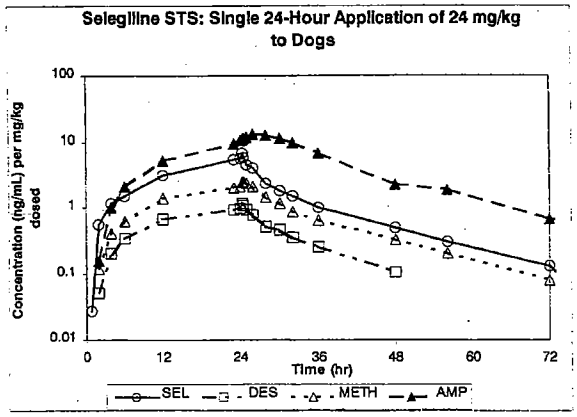

Figure 4: Mean concentrations of selegiline and metabolites after a single 24-hour application of the Selegiline Transdermal System 24 mg/kg. Concentrations are expressed per mg/kg of delivered dose based upon 20mg selegiline per patch (semilogarithmic presentation).

[06/06/00]

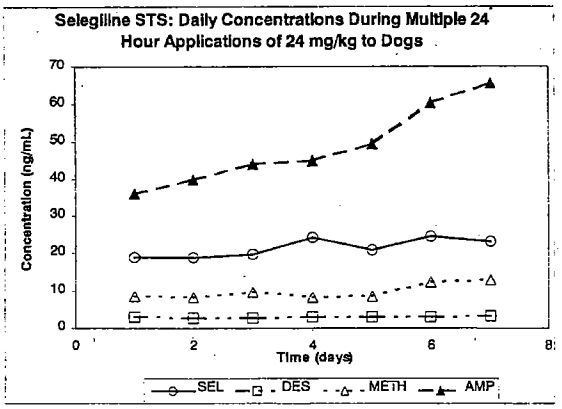

Figure 6: Mean concentrations of selegiline and metabolites at the end of dosing intervals, during multiple 24-hour applications of the Selegiline Transdermal System 24 mg/kg (Cartesian co-ordinates).

It should be noted that the plasma levels of amphetamine continued to rise over the 7-day dosing period, even though the $t_{1/2}$ estimates following acute and multiple dosing would suggest that steady-state would have been achieved by Day 7. The sponsor noted that the steady-state levels of selegiline and metabolites were higher than those achieved following a single dose. Considering the $t_{1/2}$ of all but amphetamine, these elevated steady-state levels would suggest some decrease in clearance with multiple dosing.

In Study APK-44-98B, selegiline was administered to two grps of male Beagle dogs as follows: (a) Grp 1: 3 dogs received a single dermal dose of ^{14}C-selegiline (7.2 mg/kg; in DMSO), (b) Grp 2: 3 dogs received six daily doses of selegiline via the STS (12 mg/kg), followed by a single dermal dose of ^{14}C-selegiline (7.2 mg/kg, in DMSO) on Day 7. The dose of ^{14}C-selegiline was selected to approximate the amount delivered by the STS over 24 hrs. Blood samples were collected from Grp 1 dogs at 2-168 hrs postdosing, and from Grp 2 dogs at 24 hrs post application on Days 1 and 6, and from 2-168 hrs following the dose of ^{14}C-selegiline. Urine and fecal samples were collected from Grp 1 animals over various intervals from 0-168 hrs postdosing and from Grp 2 animals over a 24-hr period o Days 1, 2, and 6, and over various intervals from 0-168 hrs following the dose of ^{14}C-selegiline on Day 7. Selegiline and metabolites were quantitated in urine and feces [using — LC/MS/MS], but not plasma. Skin at

the application site (for the STS) was excised and assayed for retained radioactivity. Plasma data were summarized in the following sponsor's table:

Table 1. Mean ± SD Concentrations of Radioactivity in Plasma of Dogs Following a Single 7.2 mg/kg Dermal Dose of ^{14}C-Selegiline HCl

Time Point (hours post dose)	Concentration of Radioactivity (μgEq/g)[1]			
	Group I		Group II	
	Mean	SD	Mean	SD
2	0.241	0.091	0.338	0.117
8	0.319	0.138	0.363	0.067
24	0.180	0.107	0.247	0.043
48	0.073	0.036	0.064	0.008
168	0.008	0.001	0.009	0.002

N=3 dogs/group

[1]Concentration based on specific activity of selegiline HCl dosing solution.

Excretion data were summarized in the following sponsor's table:

Table 2. Mean ± SD Percent Recoveries of Radioactivity in Excreta and Cage Washes Following a Single 7.2 mg/kg Dermal Dose of ^{14}C-Selegiline HCl to Dogs

Sample Type	Recovery (%)			
	Group I		Group II	
	Mean	SD	Mean	SD
Urine[1]	18.16	9.42	26.83	4.40
Feces[1]	0.93	0.19	1.65	0.46
Cage Wash[1]	1.51	1.09	2.82	1.10
Dose Site Skin	0.58	0.14	1.07	0.58
Total Recovery	21.18	9.69	32.37	3.24

N=3 dogs/group

[1]Interval = (0 –168 hours), quantitative collection for these samples.

The following metabolites (and selegiline) were detected in urine: n-desmethylselegiline, amphetamine, metamphetamine, p-hydroxyamphetamine, and p-hydroxymethamphetamine. In the samples collected on Days 1, 2, and 6, the abundance of these compounds were as follows: amphetamine = methamphetamine >> selegiline, p-hydroxyamphetamine, and N-desmethylselegiline. Selegiline, N-desmethylselegiline, and amphetamine were detected in fecal samples collected on Day 6 [Day 1 samples were not analyzed]; relative abundance of these compounds was amphetamine > selegiline > N-desmethylselegiline. In feces, amphetamine was detected only on Day 2.

Analysis of skin indicated that 0.58-1.07% of dose radioactivity was detected at the application site at 168 hrs postdosing.

Transport into the CNS in dog was assessed in Study APK-47-98B. Selegiline [24 mg/kg] was administered (via STS) to 4 male Beagle dogs for 4 days. Blood and csf samples were collected at 23-24 hrs following the last dose; samples were also collected from 2 untreated male dogs. The data were summarized in the following sponsor's table:

Table 1. Mean ± SD (N=4) Analyte Concentrations (ng/mL) in Plasma and CSF and CSF/Plasma Ratios in Dogs

Analyte	Mean ± SD Analyte Concentation (ng/mL) in Matrix 23 hour post dose Day 4		Mean CSF to Plasma Ratio
	Plasma	CSF	
Selegiline	29.8 ± 5.8	5.06 ± 1.66	0.17
N-Desmethylselegiline	3.37 ± 0.60	0.882 ± 0.187	0.26
Amphetamine	66.6 ± 37.2	67.7 ± 42.6	1.02
Methamphetamine	13.5 ± 5.8	13.4 ± 7.0	0.99

Metabolism

In vitro metabolism: metabolism of selegiline and metabolites, N-desmethylselegiline, amphetamine, and methamphetamine, by human liver microsomes was assessed in Study APK-53-98B. *In vitro* metabolism of these compounds was tested at concentrations [i.e., 15-5000] selected based on plasma levels achieved at the proposed therapeutic dose of selegiline-STS [i.e., 2, 2, 2, and 4 ng/mL for selegiline, desmethylselegiline, amphetamine, and methamphetamine, respectively]. Incubation was for 10 and 30 min. CYP P450 enzyme inhibitors were used to elucidate metabolic pathways. Results were as follows [(a)-(c) were observed using pooled human microsomes]:

(a) at 150 and 1500 nM selegiline, desmethylselegiline and methamphetamine were detected only at the higher concentration. At 150 and 1500 nM desmethylselegiline, amphetamine was detected only at the higher concentration.
(b) no metabolites were detected with 15 nM selegiline as substrate.
(c) at 1500 nM selegiline, formation of desmethylselegiline, methamphetamine, and amphetamine was linear.
(d) following incubation of 500 nM selegiline, formation of N-desmethylselegiline, methamphetamine, and amphetamine was detected. There was marked variability(7-7.5 fold) in the rates of formation of N-desmethylselegiline and methamphetamine among the 15 different microsomal samples. Formation of amphetamine was <LLOQ for 7 of the 15 samples. CYP2B6, CYP3A4/5, and CYP2C9 appeared to be involved in formation of methamphetamine from selegiline [500 nM]. No specific CYP enzyme was strongly correlated with formation of desmethylselegiline; there was a weak, statistically significant correlation of desmethylselegiline with CYP4A11 activity.
(e) following incubation of 5000 nM selegiline, formation of N-desmethylselegiline, metamphetamine, and amphetamine was detected. Rates of formation varied among the individual microsomal preparations [30- and 9-fold for desmethylselegiline and methamphetamine, respectively]. Except in one sample, the rate of amphetamine formation was considerably lower than that for the other metabolites. At the higher substrate concentration, CYP2D6 activity appeared weakly, but significantly, correlated with desmethylselegiline formation. CYP2B6 and CYP3A4/5, and to a lesser extent, CYP2C9 and CYP2A6, contributed to formation of methamphetamine. CYP2A6, CYP2B6, CYP3A4/5, and CYP2C19 were involved in formation of amphetamine.
(f) following incubation of 500 nM desmethylselegiline, only amphetamine was detected. As with metabolism of selegiline, there was a marked (20-fold) intersample variability in rate of metabolism. The primary P450 enzymes involved in formation of amphetamine were CYP2B6, CYP3A4/5, and CYP2A6.
(g) following incubation of 5000 nM desmethylselegiline, only amphetamine was detected. CYP2A6, CYP2B6, and CYP3A4/5 appeared to be the P450 enzymes primarily involved in this biotransformation.

The results of the inhibition studies are summarized in the following sponsor's tables:

TABLE 17

INHIBITION OF SELEGILINE METABOLISM IN HUMAN LIVER MICROSOMES BY ENZYME-SELECTIVE CHEMICAL SUBSTRATES OR INHIBITORS (N-DESMETHYLSELEGILINE FORMATION)

SUBSTRATE	CHEMICAL INHIBITORS							
	Conc.	100 μM EFC* **CYP2B6**	100 μM Erythromycin **CYP3A4**	100 μM TAO** **CYP3A4/5**	100 μM Nicotine **CYP2A6**	20 μM Sulfaphenazole **CYP2C9**	400 μM S-mephenytoin **CYP2C19**	1 μM Quinidine **CYP2D6**
SELEGILINE	0.5 μM †	**57.3**	**NI**	**NI**	**NI**	**NI**	**NI**	N/A
	5 μM †	**58.3**	**19.0**	**22.7**	**8.9**	**32.5**	**NI**	**NI**

† 0.5 and 5 μM selegiline = ~93 and 933 ng/mL
Values are expressed as percent inhibition
* 7-ethoxy-4-fluoromethylcoumarin
** Troleandomycin
NI : no inhibition
N/A : not applicable

TABLE 18

INHIBITION OF SELEGILINE METABOLISM IN HUMAN LIVER MICROSOMES BY ENZYME-SELECTIVE CHEMICAL SUBSTRATES OR INHIBITORS (METHAMPHETAMINE FORMATION)

SUBSTRATE	CHEMICAL INHIBITORS							
	Conc.	100 μM EFC* **CYP2B6**	100 μM Erythromycin **CYP3A4**	100 μM TAO** **CYP3A4/5**	100 μM Nicotine **CYP2A6**	20 μM Sulfaphenazole **CYP2C9**	400 μM S-mephenytoin **CYP2C19**	1 μM Quinidine **CYP2D6**
SELEGILINE	0.5 μM †	**29.6**	**NI**	**NI**	**NI**	**NI**	**NI**	N/A
	5 μM †	**50.4**	**19.7**	**28.1**	**8.7**	**37.5**	**NI**	**11.0**

† 0.5 and 5 μM selegiline = ~93 and 933 ng/mL
Values are expressed as percent inhibition.
* 7-ethoxy-4-fluoromethylcoumarin
** Troleandomycin
NI : no inhibition
N/A : not applicable

TABLE 19

INHIBITION OF SELEGILINE AND N-DESMETHYLSELEGILINE METABOLISM IN HUMAN LIVER MICROSOMES BY ENZYME-SELECTIVE CHEMICAL SUBSTRATES OR INHIBITORS (AMPHETAMINE FORMATION)

SUBSTRATES	CHEMICAL INHIBITORS							
	Conc.	100 μM EFC* CYP2B6	100 μM Erythromycin CYP3A4	100 μM TAO** CYP3A4/5	100 μM Nicotine CYP2A6	20 μM Sulfaphenazole CYP2C9	400 μM S-mephenytoin CYP2C19	1 μM Quinidine CYP2D6
SELEGILINE	0.5 μM †	ND	ND	ND	ND	ND	ND	ND
	5 μM †	55.5	4.8	25.7	12.0	NI	NI	8.2
N-DESMETHYL SELEGILINE	0.5 μM †	38.4	12.7	11.0	NI	14.0	2.7	N/A
	5 μM †	11.1	23.5	41.5	8.7	NI	NI	N/A

† 0.5 and 5 μM selegiline = ~93 and 933 ng/mL
0.5 and 5 μM N-desmethylselegiline = ~86.7 and 867 ng/mL

Values are expressed as percent inhibition.

* 7-ethoxy-4-fluoromethylcoumarin
** Troleandomycin
NI : no inhibition
N/A : not applicable
ND : No metabolites were detected

Metabolism of selegiline and desmethylselegiline by dexamethasone-induced male Sprague-Dawley rat and uninduced human liver microsomes, by "...human microsomes containing recominantly expressed CYP3Aand P450 reductase...and CYP 2D6-Val and reductase...", and by dexamethasone-induced male Sprague-Dawley rat intestinal microsomes was assessed *in vitro* in Study APK-36-95. Selegiline and desmethylselegiline (each at 50 μM) were tested alone and in the presence of various inhibitors [of CYP3A, CYP2D, CYP1A]. Both rat and human microsomes metabolized selegiline and desmethylselegiline, but not amphetamine. The data were summarized in the following sponsor's table:

Table 1: Representative metabolic profiles of selegiline and N-desmethyl selegiline in different microsomal systems.

Microsomes	Mean (SD) nmol compound in 0.5 ml incubation sample			
	Selegiline	N-Desmethyl selegiline	Methamphet-amine	Amphetamine
Selegiline substrate				
Human liver	14.9 (0.4)	4.4 (0.1)	4.6 (0.08)	0.49 (0.08)
Rat liver	13.3 (1.6)	4.3 (0.4)	4.8 (0.4)	0.59 (0.03)
CYP3A4 recomb (2 mg/ml)	21.4 (0.5)	0.37 (0.04)	0.75 (0.07)	not seen
CYP3A4 recomb (4 mg/ml)	20 (1)	0.48 (0.05)	1.08 (0.06)	not seen
CYP2D6 recomb (2 mg/ml)	23.5 (0.3)	not seen	not seen	not seen
Rat intestine (4 mg/ml)	22.9 (0.9)	0.70 (0.06)	0.74 (0.06)	not seen
N-Desmethyl selegiline substrate				
Human liver		23.1 (1.2)		4.9 (0.6)
Rat liver		17.7 (0.3)		3.5 (0.2)
Rat intestine (4 mg/ml)		28.7 (2.9)		0.14 (0.01)

Metabolism of selegiline by rat liver microsomes (particularly to methamphetamine) was inhibited by CYP3A inhibitors, diltiazem, erythromycin, and verapamil. However, in the presence of CYP3A inhibitors, ketoconazole and troleandomycin, formation of N-desmethylselegiline increased whereas that of methamphetamine was decreased. The CYP2D6 inhibitor, quinidine, had no effect on metabolism of selegiline at concentrations of 5-10 μM. At 20 μM, there appeared to be an increase in N-desmethylselegiline; however, an interfering peak precluded accurate quantitation. The CYP2D substrate, bufuralol, reduced formation of both N-desmethylselegiline and methamphetamine at 50 μM; only N-desmethylselegiline was reduced at a bufuralol concentration of 10 μM. Theophylline (CYP1A inhibitor) increased formation of N-desmethylselegiline and methamphetamine.

In human liver microsomes, formation of N-desmethylselegiline and methamphetamine were inhibited by all CYP3A inhibitors used. Formation of N-desmethylselegiline was not increased by ketoconazole and troleandomycin, in contrast to their effect in rat liver microsomes. However, in both rat and human microsomes, formation of methamphetamine was more affected than that of N-desmethylselegiline. Quinidine had only a small effect and bufuralol had no effect on metabolism of selegiline. Theophylline increased the formation of N-desmethylselegiline and methamphetamine. Metabolism by recombinant CYP enzymes was characterized by the following: (a) no metabolism of selegiline by recombinant CYP2D6, (b) complete inhibition of CYP3A4 metabolism of selegiline to N-desmethylselegiline and methamphetamine by ketoconazole, and (c) inconsistent results with quinidine.

The metabolism of selegiline by intestinal microsomes was characterized as "...very low".; however, formation of N-desmethylselegiline and methamphetamine was inhibited by ketoconazole.

Metabolism of N-desmethylselegiline to amphetamine was inhibited by CYP3A inhibitors in both rat and human liver microsomes, and (to a lesser extent) by CYP2D inhibitors in human liver microsomes. Theophylline increased formation of N-desmethylselegiline to amphetamine. The low level of N-desmethylselegiline observed in rat intestinal microsomes was due to CYP3A activity, being completely inhibited by ketoconazole.

The proposed metabolic pathways for selegiline are summarized in the following sponsor's Figure 2:

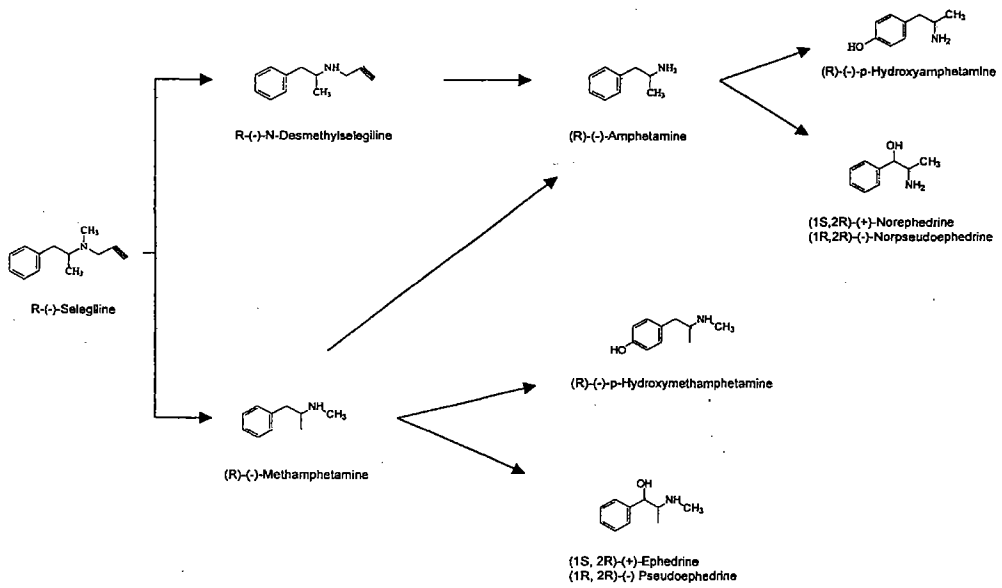

Figure 2. Potential Pathways of Selegiline Metabolism

Drug-interaction

The potential for selegiline and desmethylselegiline to inhibit selected P450 enzymes [CYP2C9, CYP2C19, CYP2B6, CYP2D6, CYP3A4/5, CYP2A6] was assessed *in vitro* using pooled human liver microsomes in Study APK-59-99B. The two compounds were tested at concentrations of 2.5-250 μM. [Positive controls were included for all enzymes tested.] Neither selegiline nor desmethylselegiline had notable inhibitory effects [i.e., <<50% inhibition at HC] on CYP2C9, CYP2B6, or CYP2A6. Selegiline and desmethylselegiline inhibited CYP2C19 activity [IC_{50}= 125 and >250 μM, respectively] and CYP2C6 [IC_{50} = 130 and 50 μM, respectively]. Selegiline and desmethylselegiline inhibited CYP3A4/5 activity by 48-49% at the HC. The sponsor concluded that the inhibitory effects of selegiline and desmethylselegiline would suggest the lack of significant clinical relevance.

Other studies

Partitioning of selegiline into rbc and plasma was assessed in blood samples from 3 human volunteers in Study APK49-98B. At concentrations of 2-500 ng/mL, selegiline distributed into rbcs "...with a partition coefficient ranging from 0.54-1.59".

The rate of release of selegiline from the STS patch — 20 mg/20 cm^2] was assessed in female Sprague-Dawley rat, female New Zealand White rabbit, and Beagle dog. Patches were collected for analysis at 2, 6, 12, and 24 hrs postdosing. In rat and rabbit, 4 animals were examined per time point; in dog, "...2 patches were removed from each dog at the same time points". The data were summarized in the following sponsor's table:

Table 1. Amount of Selegiline Released (mg) from the STS

Time Post STS Application	Amount Selegiline Released (mg)		
	Rat	Rabbit	Dog
2 hr	0.92 ± 0.211	0.69 ± 0.421	0.39 ± 0.193
6 hr	1.81 ± 0.794	1.36 ± 0.349	0.68 ± 0.178
12 hr	3.10 ± 0.780	2.31 ± 0.483	1.57 ± 0.469
24 hr	4.43 ± 0.910	3.60 ± 1.163	2.15 ± 0.475

N=8 patches/interval

Of the total drug in the patch, 22, 18, and 11% were delivered within 24 hrs postdosing in rat, rabbit, and dog, respectively. This is fairly consistent with the data provided in PK studies in rat [16-32% of patch dose] and dog [11-12% of patch dose].

PK/TK summary and conclusions: the PK of i.v. and transdermal administration of selegiline were compared in male Sprague-Dawley rat and male Beagle dog. Absolute bioavailability via the transdermal route, based on a comparison of "delivered dose", was similar in the two species [≈50-60%]. In addition, the relative (to parent compound) plasma levels of the major metabolites, N-desmethylselegiline, methamphetamine, and amphetamine, were fairly similar following i.v. and transdermal dosing in both species. However, the ratio of plasma levels of the major metabolites to parent compound [i.e., metabolite AUC/parent AUC] differed between rat and dog. In rat, plasma AUCs for N-desmethylselegiline, methamphetamine, and amphetamine, were ≈20-35% of the plasma AUC for selegiline; the relative level of N-desmethylselegiline was slightly higher following transdermal compared to i.v. dosing. In dog, plasma AUCs for N-desmethylselegiline, methamphetamine, and amphetamine, were 27-30, 70-82, and 260-300% of the plasma AUC for selegiline. In both rat and dog, ≈10-20% of patch drug content was calculated to have actually been delivered. [In a separate study, analyses of residual drug in the patch indicated that 10-30% of drug in the patch was actually delivered, with the lowest amount being in dog.] Plasma levels of selegiline and metabolites remained fairly stable

over the 24-hr dosing period in rat. [In a subsequent study in dog, plasma levels of selegiline and metabolites continued to increase over the 24-hr period.]

The PK of selegiline STS was also assessed at doses used in the definitive transdermal toxicity studies in rat and dog. In rat, PK parameters were assessed following an acute 120-mg/kg transdermal dose [the HD used in the 6-mo toxicity study]. Based on AUCs, the major circulating drug-related compound was selegiline. The primary difference between males and females was higher circulating levels of methamphetamine (2-fold) in females. Peak plasma levels of selegiline and metabolites occurred later in females [T_{max} = 2-6 and 12 hrs following patch application in males and females, respectively]. $T_{1/2}$ estimates were as follows: 1.16-1.37 hrs (selegiline), 1.08-1.29 hrs (N-desmethylselegline), 3.62-2.43 hrs (methamphetamine), 3.75-2.54 (amphetamine). In dog, PK parameters were assessed following acute and multiple [7-day] transdermal doses of 6 and 24 mg/kg [the LD and HD used in the 9-mo toxicity study]. Peak plasma levels were achieved more rapidly following multiple as compared to acute dosing. Plasma AUC_{ss} for selegiline, N-desmethylselegiline, and methamphetamine (at the LD) were ≈2-fold higher than the $AUC_{(0\text{-}24\ hr)}$ following the 1st dose, whereas the AUC_{ss} for methamphetamine (at the HD) and amphetamine were 3-4 fold higher than the $AUC_{(0\text{-}24\ hr)}$ following the 1st dose. Amphetamine was the major circulating drug-related compound at both doses following acute and multiple dosing. $T_{1/2}$ estimates were slightly shorter following multiple dosing; however, $t_{1/2}$ was longer at the HD after both acute and multiple dosing.

Mass balance studies were conducted in male Sprague-Dawley rats [48 mg/kg] and male Beagle dogs [7.2 mg/kg] using radiolabeled selegiline (dermal solution). In both species, the majority of radioactivity was recovered in the patch. Of the amount excreted, the majority of dose radioactivity was detected in urine in both rat (24-27%; acute dosing) and dog (18-27%; acute, multiple dosing). Data from one rat suggested biliary elimination of radioactivity [7% of dose radioactivity].

Tissue distribution of radioactivity following administration of radiolabeled selegiline (via application of dermal solution) was assessed in male Sprague-Dawley rats [48 mg/kg]. Radioactivity was widely distributed into tissues following both acute and multiple (6 days of unlabeled solution, followed by an acute radiolabeled STS application) dosing. Highest levels of radioactivity [2-8 hrs postdosing] were detected in liver, lacrimal glands, small and large intestine, urinary bladder [with multiple dosing], and kidney. By 24 hrs postdosing, notable levels of radioactivity were still detected in numerous tissues, but primarily in liver, kidneys, lacrimal gland, and small intestine [40, 32, 24, and 27% of peak levels, respectively]. In a separate study comparing pigmented and nonpigmented rats, tissue distribution was similar in the two strains with the exception of an increased level of radioactivity in the choroid-retina in the pigmented eye. Little or no radioactivity was detected in pigmented skin.

Distribution of unlabeled selegiline into csf was assessed in male Beagle dogs [24 mg/kg transdermal patch]. Csf levels of selegiline and metabolites were assessed 23 hrs after 4 consecutive daily doses. The major drug-related compound in both plasma and csf was amphetamine [csf:plasma = 1]. Methamphetamine levels were low [20% compared to amphetamine] in both plasma and csf [csf:plasma = 1]. Selegiline and N-desmethylselegiline levels were markedly lower in csf than in plasma, and, in csf, were only 7 and 1% of amphetamine levels.

Metabolism of selegiline was assessed *in vitro* in rat and human liver microsomes. In the *in vitro* studies, the major metabolites were N-desmethylselegiline, methamphetamine, and amphetamine. [These data confirm the findings of numerous other studies.] It was notable that there was marked variability in the rates of formation of N-desmethylselegiline and methamphetamine, and in the rate of formation of amphetamine from N-desmethylselegiline among the different microsomal samples tested. The data indicated that CYP2B6 and CYP3A4/5, and to a lesser extent CYP2C9 and CYP2A6, are involved in metabolism of selegiline to methamphetamine. CYP2B6, CYP3A4/5, and CYP2A6 are involved in the

formation of amphetamine from both N-desmethylselegiline and methamphetamine. There was no strong correlation between CYP enzyme activity and formation of N-desmethylselegiline from selegiline, although CYP2D6 activity was weakly correlated. The involvement of CYP3A in the metabolism of selegiline may be consistent with the greater metabolism of selegiline in male as compared to female rats since there are sex-related differences in activity, e.g., adult female rats do not express CYP3A2. In human liver microsomes, selegiline and N-desmethylselegiline demonstrated some inhibition of CYP2C19 and CYP3A4/5; however, the concentrations required for 50% inhibition [i.e., IC_{50} = 50 to >250 μM] would suggest the lack of a significant clinical effect. Urinary and fecal metabolites were assessed in an *in vivo* study in Beagle dog. Amphetamine was a major metabolite in both biological samples.

APPEARS THIS WAY
ON ORIGINAL

IV. GENERAL TOXICOLOGY

[Integrated summaries were provided in Sections 5A, 5C (01). Study reports were provided in Section 5C]

RAT

1. Study Title: **A 21-day range-finding toxicity study in rats with selegiline transdermal system** (Somerset Study No: TOX-534-98B, Vol 1.010/05/001743, Conducting laboratory and location: [redacted], date of study initiation: 6/98, GLP, QA:Y). **Individual data in this report were not examined.**

[Note: it appeared that some text was missing between pgs 10 and 11.]

Methods

Dosing

species/strain: Sprague-Dawley rat [redacted]
#/sex/group or time point: 5/sex/grp
age: ≈7 wks
weight: 228-265 gm for males, 157-182 gm for females
housing: "gang-housed", i.e., 2-3/cage by sex [at least during pre-dosing period]
satellite groups used for toxicokinetics: 6/sex/grp
dosage groups in administered units: 20, 40, 80, 120, 160 mg/kg/day [no control grps]
route, form, volume, and infusion rate: t.d.
duration: 21 days

Drug, lot#, and % purity: selegiline transdermal system (STS, 20 mg), STS lot no. 26E007D/selegiline lot no. 10017

Formulation/vehicle: STS, new patches were applied daily to dorsal area (≈10% of body surface) for 19-23 of 24 hrs [≥30-min drug-free period between patch applications], skin was clipped free of hair (skin was intact) prior to first application and on Days 4, 7, 11, and 15.

Observations and times:

Clinical signs: animals were observed twice daily. Application sites were examined weekly and "The most severely affected area within the test site was graded" using the Dermal Grading System (provided in Appendix B of the protocol).

Body weights: recorded prior to start of dosing, and on Days 1, 8, 15, and Day 21 of dosing, and on day of sacrifice (Day 22).

Food consumption: no.

Ophthalmoscopy: no.

ECG: no.

Hematology: no.

Clinical chemistry: blood samples were collected (via orbital plexus) on Day 22 for analysis of the following parameters: ALT, albumin, A/G ratio, alkaline phosphatase, AST, Ca, cholesterol, creatinine, Na, K, Cl, globulin (calculated), glucose, P_i, total bilirubin, total serum protein, urea N.

Urinalysis: no.

Gross pathology: a complete necropsy was performed on all main-study animals.

Organ weights: no.

Histopathology: no.

Toxicokinetics: blood samples were collected at 0,25, 1, and 4 hrs post-application from 3/sex/grp and at 0.5, 2, and 12 hrs post-application on Days 1 and 21. Plasma levels of selegiline "and its metabolites" were quantitated using a validated GC method with

detection [LLOQ = — ng/mL]. Analyses were performed by

Results

Mortality: 4 TK animals were found dead [2 M at 120 mg/kg: Day 21; 1 F at 80 mg/kg: Day 21; 1 F at 160 mg/kg: Day 22]. Necropsy findings consisted of the following:

120 mg/kg: "...ocular opacity, wet red mating around the mouth, a small amount of dark red gelatinous material in the esophagus, red fluid mixed with ingesta in the stomach, dark red foci on the lungs, and reddened mandibular lymph node" in 1 M, and "...wet red matting around the eyes..." in 1 M.

80 mg/kg: "...ocular opacity, mottled liver, and wet red matting around the nose, mouth and eyes".

160 mg/kg: "...scabbing at the test site and an eye lesion (i.e., hard and blackened with surrounding harderian gland dark red; probably due to orbital bleeding)".

There were no unscheduled deaths in main-study animals. The sponsor attributed deaths in the TK animals to trauma associated with blood collection.

Clinical signs: clinical signs were observed at all doses. Primary signs consisted of local irritation,"dark material" around the eyes and/or nose, urine stain, and, in females at 120 and 160 mg/kg, swollen/red eyelids. Local effects consisted of "slight erythema" in males (80, 120, and 160 mg/kg) and females (all doses) and "desquamation" in females at 20 (1F), 80 (1F), and 160 (3F) mg/kg.

Body weights: mean body wt loss was noted in males (all doses) and in females at 20, 40, and 80 mg/kg during the first 8 days of dosing. However, thereafter mean body wt gain was noted. Final body wts in males were 17, 20, 14, 13, and 16% higher relative to Day 1 at 20, 40, 80, 120, and 160 mg/kg, respectively. In females, mean final body wts were 10, 9, 10, 7, and 9% higher relative to Day 1 at 20, 40, 80, 120, and 160 mg/kg, respectively.

Clinical chemistry: there were no clear differences among grps on any of the parameters analyzed.

Gross pathology: the only dose-related finding was "dark material" on the "haircoat". In males, this finding was detected in 1/5 HDM; in females, 1/5, 2/5, and 3/5 animals were affected at 80, 120, and 160 mg/kg. Scabbing at the periphery of the application site was detected at all doses (no dose-related incidence) in males and females.

Toxicokinetics: it was noted that there was insufficient sample volume "For a substantial number of samples.." to allow quantitation of plasma drug levels. The report was poorly organized, with no page numbers by which to locate summary data. The report noted that plasma concentrations of selegiline and "the three metabolites increased in a dose-related manner". Plasma selegiline levels were noted to increase "...rapidly over the first two hours after...application and were maintained out to 12 hours, the last sampling time". The T_{max} for oral selegiline has been reported to be 15 min [first sampling time]. At 120 mg/kg, plasma levels of selegiline (males and females combined) were similar to those previously reported following an oral 100 mg/kg dose. On Day 21, mean plasma selegiline levels at 120 mg/kg were 12.4, 46.3, 83.2, 113, 100.2, and 71.0 ng/mL at 0.25, 0.5, 1, 2, 4, and 12 hrs post-application, respectively. [The steady-state plasma selegiline level in elderly men at the proposed clinical dose was 2.72 ng/mL.]

Plasma levels of N-desmethylselegiline at 120 mg/kg on Day 21 were as follows (M + F): <LLOQ-4.8, 4.6-12.0, 7.3-19.7, 17.2-28.4, 13.5-28.1, and 18.8-23.6 ng/mL at 0.25, 0.5, 1, 2, 4, and 12 hrs post-application, respectively.

Plasma levels of l-amphetamine at 120 mg/kg on Day 21 were as follows (M + F): 7.2-22.8, 9-18.5, 10.9-25.0, 18.1-29.2, 18.4-36.9, and 20.6-42.6 ng/mL at 0.25, 0.5, 1, 2, 4, and 12 hrs post-application, respectively.

Plasma levels of l-methamphetamine at 120 mg/kg on Day 21 were as follows (M + F): 7.3-11.3, 8.2-18.8, 12.7-30.8, 29.3-59.8, 37.5-51.8, and 34.6-65.0 ng/mL at 0.25, 0.5, 1, 2, 4, and 12 hrs post-application, respectively.

2. Study Title: **A 21 day oral (gavage) range-finding toxicity study with selegiline hydrochloride** (Somerset Study No: TOX-535-98B, Vol #1.028, Conducting laboratory and location: [redacted], date of study initiation: 6/98, GLP, QA:Y)

Methods

Dosing

species/strain: Sprague-Dawley rat [redacted]
#/sex/group or time point: 5/sex/grp
age: ≈7 wks
weight: 214-261 gm for males, 169-206 gm for females
satellite groups used for toxicokinetics: 6/sex/grp [one F was reassigned to the main-study grps to replace a main-study female removed from the study due to "an apparent broken right hindlimb"].
dosage groups in administered units: 20, 40, 60, 80, 100 mg/kg
route, form, volume, and infusion rate: oral (gavage), 10 mL/kg

Drug, lot#, and % purity: selegiline HCl, lot no. 9706011, [redacted] total impurities (CoA).

Formulation/vehicle: solution/distilled water (formulation prepared fresh daily, and stirred continuously during the dosing procedure).

Observations and times:

Clinical signs: animals were observed daily for clinical signs, approximately 0.5-2 hrs postdosing.
Body weights: body wts were recorded on Days 1, 8, 15, and 21 of dosing, and on day of sacrifice.
Food consumption: no.
Ophthalmoscopy: no.
ECG: no.
Hematology: no.
Clinical chemistry: blood samples were collected (via orbital plexus) on Day 22 of dosing for analysis of the following parameters: ALT, albumin, A/G ratio, alkaline phosphatase, AST, Ca, cholesterol, creatinine, Na, K, Cl, globulin (calculated), glucose, P_i, total bilirubin, total serum protein, urea N.
Urinalysis: no.
Gross pathology: a complete necropsy was performed on all animals on Day 22.
Organ weights: no.
Histopathology: no.
Toxicokinetics: blood samples were collected in satellite animals on Days 1 and 21 at 15min, 1 and 4 hrs postdosing in one set of animals [3/sex/grp] and at 30 min, 2 and 12 hrs postdosing on a 2nd set of 3/sex/grp. Plasma samples were sent to [redacted] for analysis. [TK animals were observed for general health daily, weighed on Days 1, 8, 15, and 21 of dosing, and examined for gross lesions.]

Results

Mortality: there were 5 unscheduled deaths during the study. Of these, 3 occurred in satellite

animals [1F at 20 mg/kg, 1F at 60 mg/kg, 1F at 100 mg/kg]. In two cases, death was determined to be due to dosing trauma. No cause of death was determined in the HDF (death on Day 2); "dark red lungs" were observed at necropsy.

Two main-study animals died [1 F at 80 mg/kg, 1 F at 100 mg/kg]; both were found dead on Day 5 of dosing. No clinical signs were observed in these animals prior to death. The sponsor did not rule out drug as a cause of death. Therefore, in females, there were spontaneous deaths (not attributed to dosing error) in 1 F at 80 mg/kg and 2 F at 100 mg/kg.

Clinical signs: clinical signs were evident at all doses. At 20 mg/kg, the only clinical sign observed was salivation which was noted in 2/5 males. At 40 mg/kg, salivation was noted in both males and females. At 60, 80, and 100 mg/kg, clinical signs consisted of salivation, dark material around the nose and mouth (dose-related only in males), and increased activity upon handling. At 100 mg/kg, increased activity upon handling occurred in 4/5 M and 4/4 F.

Body weights: compared to the LD grps (no C grps were included), mean body wt was reduced in a dose-related manner in males; final mean body wts were reduced by 9, 11, 13, and 16% relative to the LD. In females, mean body wt tended to be lower at doses >LD compared to the LD grp; however, the decrease was not dose-related. Mean body wt gain was reduced (compared to the LD) primarily during the first wk of dosing. Mean body wt loss was noted at the HD in males during this period. Mean body wt gain during the last 2 wks was not clearly affected by drug.

Clinical chemistry: there were no clear drug-related effects. The values of some parameters were elevated in individual animals; however, the small number of animals per grp and the lack of C grps made the data difficult to evaluate.

Gross pathology: the only finding noted in the main-study HDF that died was wet matting on haircoat; no gross findings were noted in the 80-mg/kg F that died. There were no clear findings in survivors. Dark material and/or hair loss was noted on the haircoat in males at 60-100 mg/kg; dark material on the haircoat was noted in 1/4 HDF, and hair loss was noted in 1 F at 80 mg/kg.

Toxicokinetics: data were to be reported in a separate study report.

3. Study Title: **A six month toxicity study in rats with selegiline transdermal system** (Somerset Study No. TOX-537-98B, Vol. 1.012/05/002498, Conducting laboratory and location: [redacted], date of study initiation: 12/98, GLP, QA:Y)

Methods

Dosing

species/strain: Sprague-Dawley rat [redacted]

#/sex/group or time point: 20/sex/grp

age: ≈8 wks

weight: 177-231 gm for males, 149-185 gm for females.

housed: individually

satellite groups used for toxicokinetics or recovery: 8/sex/grp for TK, 5/sex/grp for 1-mo recovery.

dosage groups in administered units: 0 (untreated), 0 (placebo), 30, 60, 120 mg/kg

route, form, volume, and infusion rate: td [20 mg patch]

duration: 6-mo; animals were not dosed on Days 26, 27, and 28 "due to inclement weather".

Drug, lot#, and % purity: STS, STS lot nos. 26E007D and 26E006L, selegiline lot nos. 10017 and 10027, purity = [redacted]

Formulation/vehicle: t.d. patch. A new patch applied each day, skin was clipped free of hair with skin intact. Patch covered ≈10% of body surface, and remained in place 22-24 hrs/day. Patches were held in place with [redacted] and athletic tape. Patches were checked twice per day. Intact patches that fell off were replaced when possible; patches that were destroyed were not replaced.]

Observations and times:

Clinical signs: animals were observed twice daily. Application sites were examined weekly and at sacrifice. Findings were scored using the Macroscopic Dermal Grading System.

Body weights: recorded prior to the first application, weekly during the dosing period, and at sacrifice.

Food consumption: recorded on Day 1 and weekly during the dosing period.

Ophthalmoscopy: performed on all animals prior to the first application, and "when possible" on 10/sex/grp on Day 94 and Day 179. Pupils were dilated with 0.5% Mydriacyl prior to examination [biomicroscopy, indirect ophthalmoscopy].

ECG: no

Hematology: blood samples were collected (via orbital plexus)from 10/sex/grp on Day 93/94 [main-study animals] and Day 177-179 [main-study and the recovery animals], and on Day 211 [recovery animals] for analysis of the following parameters: rbc ct, hct, hgb, MCH, MCHC, MCV, platelet ct, wbc (ct, differential), [reticulocyte slides prepared but not examined]. Blood samples were collected (posterior vena cava) on Day 183/184 [main-study animals] and Day 213 [recovery animals] for analysis of coagulation parameters [PT, APTT, fibrinogen].

Clinical chemistry: blood samples were collected from 10/sex/grp on Day 93/94 [main-study animals] and Day 177-179 [main-study and the recovery animals], and on Day 211 [recovery animals] for analysis of the following parameters: ALT, albumin, A/G ratio, AST, Ca, cholesterol, creatinine, globulin (calculated), glucose, Na, K, Cl, P_i, total bilirubin, total serum protein, urea nitrogen.

Urinalysis: urine samples were collected overnight from 10/sex/grp [main-study animals] on Day 93-95], Day 177-179 [main-study and recovery animals], and Day 211-212 [recovery animals] for analysis of the following parameters: volume, color, appearance, pH, specific gravity, protein, glucose, ketones, urobilinogen, nitrites, bilirubin, occult blood, wbcs, microscopic analysis of sediment.

Gross pathology: a complete necropsy was performed on all animals.

Organ weights: wts of the following organs were recorded in survivors: liver, kidney, adrenal gland, testis, ovary, brain, thyroid/parathyroid, heart.

Histopathology: the following tissues were examined microscopically in all C [untreated, placebo] and HD animals (main-study and recovery), and all LD and MD animals found dead: epididymides, seminal vesicles, prostate, uterus, vagina, adrenals, gross lesions, aorta, brain [medulla/pons, cerebellar cortex, cerebral cortex], cecum, colon, duodenum, esophagus, exorbital lacrimal gland, eyes/optic nerve, femur/bone marrow, heart, ileum, jejunum, kidney, liver [3 sections], lungs/bronchi, mammary gland, mesiastinal lymph node, mesenteric lymph node, pancreas, peripheral nerve (sciatic) pituitary, rectum, skeletal muscle (thigh), spinal cord (cervical, midthoracic, lumbar), spleen, sternum/bone marrow, stomach (glandular/nonglandular), submandibular lymph node, submaxillary salivary gland, testis/ovary, thymus, thyroid/parathyroid, tongue, trachea, treated skin, untreated skin (hip area), urinary bladder. In addition, the following tissues were examined microscopically in all LD and MD animals: treated skin [main-study animals], lung, liver, kidney, gross lesions. Kidney, liver, lung/bronchi, and gross lesions were examined in LD and MD recovery grps. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with H & E for examination. Histopathological analysis was conducted by [redacted]

microscopic analysis was performed by Dr. [redacted], board-certified veterinary pathologist.

Toxicokinetics: blood samples were collected from satellite animals [8/sex/grp] on Days 1 and 183 at 0.5, 2, 4, 6, 12, and 24 hrs post-application, and 23 hrs post-application on Days 14, 42, 70, 98, 126, and 154. Methods and data were provided in a separate appended report.

Results

Administer doses: administered doses were estimated to be as follows: LDM (20.2-40.0 mg/kg), MDM (48.3-72.1 mg/kg), HDM (107.0-131.6 mg/kg), LDF (20.2-40.7 mg/kg), MDF (48.3-72.1 mg/kg), HDF (104.2-134.2 mg/kg). Selected patches were retained during dosing of satellite-TK animals for analysis; however, patches were not analyzed. Therefore, "delivered doses" were not estimated.

Mortality: there were 7 unscheduled deaths: 3 LDM (Day 142, 15, 131), 1 CF(untreated) (Day 94), 1 CF(placebo) (Day 178), 1 LDF (Day 57), and 1 MDF (Day 105). These 7 animals were found dead. According to the sponsor, "The deaths were attributed to natural causes or the binding procedures used to maintain the patches in place, rather than to treatment with the placebo or Selegiline patches". There didn't appear to be any notable differences in the clinical signs observed in these animals as compared to survivors.

Clinical signs: selected clinical signs are summarized in the tables below [CU = untreated C, CP = placebo control; data expressed as no. of episodes (i.e., days)/no. of affected animals)]. Notable is the number of days/animals in which patches were not in place and had to be either reapplied or destroyed. [From the individual tables it could not be determined what proportion of the applied patches (when necessary, the 20-mg patches were cut into pieces in order to apply the appropriate dose) were involved in each case.] The sponsor concluded that "Occasionally binders/patches were found off males and females in the placebo patch control, 30, 60, and 120 mg/kg/day groups during the treatment period. The incidence of these findings did not follow any consistent or dose-related pattern. Since an analysis of the toxicokinetics showed that blood levels were consistent in all treated groups during the study, this finding is not considered to have affected the results of the study". In male, the mean (range) number of days on which either the patch was listed as reapplied [suggesting some decrease in dose] or destroyed were as follows: CP [14 (4-27)], LD [6 (1-17)], MD [6 (0-15)], and HD [4 (0-27)]. In only 1 treated animal [HD, main-study] was the number of days ≥20 [i.e. ≈10% of total days].

MALES

SYSTEM	SIGN	CP	CU	LD	MD	HD
DAYS 1-185						
activity	overt aggressiveness	0/0	0/0	1/1	2/2	19/12
body	scab(s)	8/7	27/9	36/13	54/18	55/17
	hairloss	26/7	62/10	90/13	108/17	86/19
	urine stains	1/1	1/1	3/3	4/3	35/15
eye	reddened eyelid(s)	1/1	6/1	4/2	14/5	7/4
	dark material around	6/5	27/6	13/8	15/11	44/15
	periorbital swelling	1/1	0/0	2/2	0/0	3/3
nose/mouth	dark material around nose	53/16	35/16	97/23	105/22	232/23
	dark material around mouth	4/4	0/0	7/7	15/8	31/12
	malalignment	1/1	14/3	4/2	26/5	12/7
	broken incisor(s)	1/1	0/0	6/3	14/5	8/5
other	patch reapplied	148/25	--	59/19	51/14	30/12
	patch destroyed	197/25	--	86/23	89/21	73/20
post-dose	tremors	0/0	0/0	0/0	0/0	2/2
	wobbly gait	0/0	0/0	0/0	0/0	3/2
RECOVERY						
body	hairloss	0/0	1/1	0/0	4/1	6/3
eye	lesion	0/0	0/0	0/0	0/0	5/1

In females, the mean (range) number of days on which either the patch was listed as reapplied [suggesting some decrease in dose] or destroyed were as follows: CP [11 (0-76)], LD [8 (0-28)], MD [11 (0-56)], and HD [14 (0-55)]; the number of animals in which [HD] was the number of days ≥20 [i.e., ≈10% of total days] was as follows: 3/25 CP, 3/25 LD, 5/25 MD, 7/25 HD]. All but one of these females were main-study animals.

FEMALES

SYSTEM	SIGN	CP	CU	LD	MD	HD
DAYS 1-185						
activity	overt aggressiveness	0/0	0/0	0/0	0/0	26/14
body	scab(s)	36/15	33/13	38/19	59/20	44/16
	hairloss	79/13	12/3	164/21	166/17	162/19
	urine stains	7/5	1/1	4/3	7/5	154/22
eye	reddened eyelid(s)	22/9	5/2	12/8	17/10	15/10
	periorbital swelling	1/1	1/1	1/1	1/1	0/0
nose/mouth	dark material around nose	58/22	30/18	67/19	64/17	180/24
	dark material around mouth	8/7	0/0	4/4	5/3	26/14
	malalignment	0/0	8/3	2/2	5/4	1/1
	broken incisor(s)	1/1	5/2	1/1	8/2	6/5
other	patch reapplied	43/12	--	31/13	53/12	35/12
	patch destroyed	234/19	--	177/23	216/20	316/22
post-dose	tremors	0/0	0/0	0/0	1/1	5/4
	wobbly gait	0/0	0/0	0/0	1/1	5/4
	vocalization	0/0	0/0	0/0	1/1	5/5
RECOVERY						
body	hairloss	0/0	5/1	4/2	11/4	9/2
eye	lesion	0/0	4/1	5/1	0/0	0/0

Examination of the application site indicated local irritation in all groups (excluding untreated Cs). However, the incidence and/or severity of erythema, eschar, and

desquamation were increased in HDM and HDF. In males, desquamation was also increased at the lower doses. In females, there were increases in grade 1 erythema at the lower doses, and in grade 1 eschar and in desquamation at the MD. Also in females, there was an increase in "maximized grade 4" at the HD; however, to what this term refers is unclear. The sponsor noted that the scale for evaluation of dermal changes was provided in Appendix C; however, only Certificates of Analyses for the patch lots were provided in Appendix C. No signs of dermal irritation were noted during the recovery period.

Body weights: mean baseline body wts were the same in all groups in males (i.e., 200 gm; range of SD: 11.8-13.1 gm) and females (166 gm; range of SD: 9.0-9.5 gm). An examination of the individual data indicated a range of body wts in all groups; therefore, it is possible that this remarkable similarity among grps is a result of carefully selected populations of rats.

In males, mean body wt was significantly increased (16-31%) in the untreated C relative to the placebo C grp, i.e., daily application of the patch appeared to result in a significant decrease in mean body wt. Relative to the placebo C grp, mean body wt was reduced throughout the dosing period in HDM (4-10%), and during the first 2 mo in MDM. At the end of the dosing period, mean body wt was 27% higher in untreated CM and reduced by 9% in HDM compared to placebo CM. Mean body wt gain was highest in the untreated C grp, and lowest in the MD and HD (particularly during the 1st and 4th wks); mean body wt gain was not consistently affected throughout the dosing period. There were no significant differences among groups during recovery; however, the tendency for mean body wt to be higher (13%) in the untreated CM-R and lower (8%) in HDM-R (relative to the placebo C) remained.

In females, mean body wt was significantly increased (11-27%) in the untreated C relative to the placebo C grp. Relative to the placebo C grp, mean body wt was reduced at the HD (3-8%), the effect being significant only on Days 7, 14, 28-49, and 84. At the MD, mean body wt was significantly reduced (compared to placebo) only on Day 28 (5%). Mean body wt gain was highest in the untreated C grp during Wks 1, 2, 4, and 5, and sporadically thereafter), and reduced in all dose grps (compared to the placebo C) during the first wk. Mean body wts were similar among grps during the recovery period.

Food consumption: in males, food consumption was reduced at the MD and HD throughout most of the dosing period. However, food intake was increased in untreated CM only during the first wk of dosing; from Day 98 on, mean food intake was actually reduced (compared to placebo CM) in untreated CM. During the recovery period, food intake was consistently reduced in untreated CM. In females, the only fairly consistent effect was a decrease in food intake in untreated CF (compared to placebo CF); however, food intake was increased slightly (15%) in this grp during the first wk. During the recovery period, food intake in untreated CF remained lower compared to the other grps.

Ophthalmoscopy: animals were examined by a board-certified veterinary ophthalmologist. In the examination conducted prior to the start of dosing, the ophthalmologist reported a high incidence of dacryoadenitis. According to the report, "The cause of the dacryoadenitis is not apparent. The number of affected animals is extremely unusual. The clinical appearance is a red-brown discharge soiling the periocular area. Many of the animals exhibit mild squinting and generalized corneal dryness." Since the body wrap was applied prior to the examination, the ophthalmologist concluded that it might be the cause of the findings. Other possible causes are "...viral infection or other environmental irritants...". All findings observed during the dosing period were

considered unrelated to drug. [No incidence of dacryoadenitis was reported on Day 94 or 179, even though animals were continuously wrapped.]

Hematology: there were no clear drug-related effects.

Clinical chemistry: there were no clear drug-related effects. In males, glucose was increased in untreated C (relative to placebo CM), Ca was slightly (but significantly; 3-6%) increased in all grps at one or both sampling times (during dosing) relative to placebo CM, and P_i was increased in all dosed grps during Days 177-179 [6-10%, dose-related] and during the recovery period [12, 17, 14% at LD, MD, HD, respectively].

In females, there were a number of effects in untreated Cs [relative to placebo CF; e.g., elevated glucose (48-28%)]; however, there were no clear drug-related effects (comparing dosed grps to placebo C).

Urinalysis: in males, the only notable effect was a decrease in urinary volume in MDM and HDM on Day 93-95 (33 and 56%, respectively), and at all doses (33%) on Days 177-179. In recovery animals, urinary volume was similar or higher in dosed grps relative to Cs. In females, urinary volume was decreased at the MD and HD on Days 93-95 (57%), and at all doses on Day 177-179 (50, 38, 62% at LD, MD, HD, respectively). Urinary volume was similar or higher in dosed grps (relative to Cs) during the recovery period.

Organ Weights: in males, there were no clear drug-related findings, except for those associated with body wt changes. For example, absolute wts of a number of organs (e.g., thyroid, heart, liver) were increased whereas relative wts of these organs were decreased in untreated CM. Also, absolute wts of kidney and liver were reduced in HDM, although relative wts of these organs were unaffected. In recovery males, there were no clear drug-related findings.

In females, findings consisted of the following: (a) a decrease in absolute and relative adrenal wt; absolute adrenal wt was reduced at all doses (12-16%; not dose-related) whereas relative wt was decreased in untreated CF (28%) and all dosed grps (8-16%, not dose-related), (b) absolute liver wt was increased in all grps relative to placebo C (8-12%); relative liver wt was increased in all dosed grps (8, 12, and 14% at LD, MD, and HD, respectively). In recovery females, there was a significant increase in absolute and relative liver wt at the HD (19-17%).

Gross pathology: in the animals found dead, findings were as follows: (a) in 1 LDM, mottled lung, dilated renal pelvis, and a thoracic cavity adhesion ("involving a portion of the left ventricle, pericardium and left lung lobe") were detected; a misshapen liver was noted in another LDM. (b) in the control animals, findings consisted of mottled lung, stomach foci, and/or fluid contents in the abdominal cavity; the untreated CF also had a mass (characterized as "nonspecific"). (c) in the LDF, dark material on the fur, skin scabs, enlarged lymph nodes, body fat depletion and dehydration, fluid in the thoracic cavity, and a thymic mass were detected. (d) in the MDF, the only finding was muscle hemorrhage. Most gross findings in survivors were unremarkable; the only apparently drug-related findings in survivors consisted of dark material on the fur/hairloss (increased at HD), skin scabbing (LDF, MD, HD), broken incisor(s) (MDM, HDM), and small/soft testes (1HDM). There were no remarkable findings in recovery animals.

Histopathology: according to the study pathologist, drug-related findings (also noted in placebo C grps) were limited to application site, i.e., hyperkeratosis and epidermal hyperplasia. The incidence and severity of these findings are summarized in the following table, along with a few other notable findings. [There were no notable findings in recovery animals.] The study pathologist stated that "Epidermal hyperplasia was completely reversible after a 30-day recovery period; none of the rats from the placebo control or 120 mg/kg/day groups had this lesion after the recovery period". Marked hyperkeratosis and moderate

epidermal hyperplasia was detected in 1/5 HDM-R; however, the location in which these skin findings were observed was not specified except that it was not listed at either "treated" or "untreated" skin.]

TISSUE	FINDING	MALES					FEMALES				
		CP	CU	LD	MD	HD	CP	CU	LD	MD	HD
MAIN STUDY											
lung	hemorrhage										
	minimal	0/20	1/20	0/20	2/20	3/20	0/20	0/20	0/20	1/20	0/20
	mild	0/20	0/20	0/20	0/20	0/20	1/20	0/20	0/20	0/20	0/20
	perivasc inflam infiltrate										
	minimal	0/20	0/20	0/20	2/20	3/20	0/20	1/20	0/20	2/20	2/20
lymph node (mediastinal)	hemorrhage										
	minimal	4/20	2/20	1/3	--	3/20	5/20	10/20	0/1	0/1	1/20
	mild	1/20	1/20	0/3		4/20	3/20	3/20	0/1	0/1	3/20
	moderate	1/20	0/20	1/3		2/20	2/20	4/20	0/1	0/1	5/20
lymph node (submandib)	hemorrhage										
	minimal	1/20	2/20	1/3	--	2/20	1/20	0/20	0/1	0/1	4/20
		0/20	0/20	0/3		0/20	0/20	1/20	0/1	0/1	0/20
skin (treated)	hyperkeratosis										
	minimal	2/20		0/20	0/20	1/20	0/20		0/20	0/20	2/20
	epidermal hyperplasia										
	minimal	7/20		12/20	9/20	13/20	12/20		10/20	14/20	8/20
	mild	0/20		0/20	0/20	6/20	1/20		4/20	4/20	12/20
testes	tubular atrophy, asperm.										
	marked	0/20		0/20	0/20	1/20					
uterus	dilatation										
	minimal						1/20	0/20	0/1	0/1	0/20
	mild						5/20	1/20	0/1	0/1	1/20
	moderate						3/20	1/20	0/1	0/1	3/20
	marked						0/20	0/20	0/1	0/1	6/20

Toxicokinetics: the data are summarized in the following sponsor's tables:

Table 1. Mean ± SD of plasma concentration of selegiline and its metabolites 23 hours after application of the patch on selected dosing days.

	Mean ± SD Analyte Concentration (ng/mL) 23 hr post dose Days 1-154							
	Selegiline		N-Desmethylselegiline		Amphetamine		Methamphetamine	
Dosage Level	M	F	M	F	M	F	M	F
30 mg/kg/day	12.1 ± 6.2	11.3 ± 4.4	2.97 ± 1.28	2.65 ± 1.08	3.16 ± 1.43	4.32 ± 2.18	2.99 ± 1.40	5.20 ± 2.41
Metabolite/ Selegiline Ratio	1	1	0.25	0.23	0.26	0.38	0.25	0.46
60 mg/kg/day	22.9 ± 7.3	24.2 ± 7.1	5.42 ± 1.72	6.18 ± 2.04	5.81 ± 1.71	13.7 ± 5.6	5.69 ± 1.86	15.2 ± 5.4
Metabolite/ Selegiline Ratio	1	1	0.24	0.26	0.25	0.57	0.25	0.63
120 mg/kg/day	49.7 ± 12.5	48.9 ± 13.8	8.74 ± 2.59	12.2 ± 4.6	13.5 ± 4.6	22.7 ± 9.3	13.1 ± 4.8	27.7 ± 10.4
Metabolite/ Selegiline Ratio	1	1	0.18	0.25	0.27	0.46	0.26	0.57

Table 2. Toxicokinetic parameters in rats following application of Selegiline Transdermal System.

Dose (mg/kg/day)	Pharmacokinetic Parameter	Selegiline Composite (N=6) Parameter Value (Male and Female Combined)	
		Day 1	Day 182
30	Cmax ng/mL	22.1	25.3
	Tmax hr	6	4
	AUC(0-24) ng•hr/mL	379	412
	Css ng/mL	not applicable	17.2
60	Cmax ng/mL	57.9	50.6
	Tmax hr	6	6
	AUC(0-24) ng•hr/mL	969	879
	Css ng/mL	not applicable	36.6
120	Cmax ng/mL	117	120
	Tmax hr	6	4
	AUC(0-24) ng•hr/mL	2066	2277
	Css ng/mL	not applicable	94.9

DOG

Study Title: **A nine month dermal toxicity study in dogs with selegiline transdermal system** (Somerset Study No: TOX-538-98B, Vol #1.020, Conducting laboratory and location: —— , TK and patch analyses conducted by —— , date of study initiation: 10/26/98, GLP, QA:Y)

Methods

Dosing

species/strain: Beagle dogs ——

#/sex/group or time point: 4/sex/grp

age: ≈5.5 mo

weight: ≈8-10.2 kg for males, ≈6.1-9.1 kg for females.

satellite groups used for toxicokinetics or recovery: 2/sex/grp for 1-mo recovery.

dosage groups in administered units: 0 (untreated), 0 (placebo), 6, 12, 24 mg/kg/day. The HD was physically limited by the number of patches that could applied. The doses used corresponded to 3 (LD), 6 (MD), and 12 (HD) patches for a 10 kg dog. The HD was expected to produce "toxic effects, but not excessive lethality".

route, form, volume, and infusion rate: transdermal

Drug, lot#, and % purity: selegiline, drug lot nos. 10017 (STS lot no. 26E007D), 10027 (STS lot no.26E006L). Purity of test article patches: —— for STS lot no. 26E007D and 26E006L, respectively.

Formulation/vehicle: transdermal patch (20 mg selegline/20 cm^2 patch). Patches were applied fresh daily (dorsal, mid-dorsal area) to areas of intact skin clipped free of hair "...prior to the first application...and when necessary thereafter". Patches were held in place with ".. —— and/or double stick athletic tape. A stockinette/spandex jacket and a cervical collar were utilized to prevent disruption of the test/control materials". Patches were maintained in place for 22-24 hrs, except on days on which biological samples were collected for analysis of clinical pathology and/or TK analysis. On those days, patches were removed for a longer period, exceeding 3 hrs. Patches were checked twice per day.

Observations and times:

Clinical signs: animals were checked daily for clinical signs; a more extensive clinical

examination was performed weekly and a "detailed" physical examination was performed monthly. Local irritation was assessed weekly during the dosing and recovery periods using "the Dermal Grading System".

Body weights: body wts were recorded prior to start of dosing, and weekly during the dosing and recovery periods.

Food consumption: food intake was recorded daily prior to start of dosing and during the dosing and recovery periods.

Ophthalmoscopy: examinations were performed in main-study and recovery animals prior to start of dosing and on Days 89, 184, and 265, and in recovery animals on Day 301. Pupils were dilated with Mycriacyl® prior to examination.

ECG: ECG and blood pressure were recorded on main-study and recovery animals prior to start of dosing, and on Days 32, 93, 183, and 272, and in recovery animals on Day 303. ECG recordings were generated using leads I, II, III, aV_R, aV_L, and aV_F; however, only lead II was examined unless findings were noted.

Hematology: blood samples were collected (via the jugular vein) prior to start of dosing, and on Days 33/34, 180/181, and 274/276 in main-study and recovery animals, and on Days 306/307 in recovery animals for analysis of the following parameters: rbc ct, hct, hgb, MCH, MCHC, MCV, platelet ct, wbc (ct, differential), APTT, PT.

Clinical chemistry: blood samples were collected (via the jugular vein) prior to start of dosing, and on Days 33/34, 180/181, and 274/276 in main-study and recovery animals, and on Days 306/307 in recovery animals for analysis of the following parameters: A/G ratio, ALT, albumin, alkaline phosphatase, AST, Ca, cholesterol, creatinine, CPK, Na, K, Cl, GGT, globulin (calculated), glucose, LDH, P_i, total bilirubin, total serum protein, BUN.

Urinalysis: urine samples were collected (overnight) prior to start of dosing, and on Days 33/34, 89/90, 180/182, and 274/276 in main-study and recovery animals, and on Days 306-307 in recovery animals for analysis of the following parameters: volume, bilirubin, blood, glucose, gross appearance, ketones, pH, protein, specific gravity, and microscopic analysis of sediment.

Gross pathology: a complete necropsy was performed on all animals.

Organ weights: wts of the following organs were recorded in all animals: adrenal gland, brain, epididymides, heart, kidneys, liver, lungs, ovaries, thyroid/parathyroid, pituitary, uterus, prostate, testes.

Histopathology: the following tissues were examined microscopically in main-study animals only: epididymides, prostate, uterus, vagina, adrenals, gross lesions, aorta, bone marrow, brain [sections of medulla/pons, cerebellar cortex, cerebral cortex], cecum, colon, duodenum, esophagus, eyes/optic nerve, femur (surface, bone marrow), gallbladder, heart, ileum, jejunum, kidneys, larynx, liver [2 lobes, 3 sections], lungs (infused with formalin)/bronchi, mammary gland, mandibular salivary gland, mediastinal lymph node, mesenteric lymph node, pancreas, sciatic nerve, pituitary, rectum, skeletal muscle (thigh), treated skin, untreated skin, spinal cord [cervical, midthoracic, lumbar], spleen, sternum/bone marrow, stomach, submandibular lymph node, testes, ovary/oviducts, thymus, thyroid/parathyroid, tongue, trachea, urinary bladder. Tissues were preserved in 10% neutral buffered formalin, sectioned, and stained with H & E for examination. Recovery animals were not examined microscopically since, according to the sponsor, there were no drug-related findings in main-study animals. Histopathology was performed by [redacted]. According to the Pathologist's report, 4 "treated skin sites" were examined per animal; these were designated dorsal thoracic surface 1 and 2 L (left) and 1 and 2 R (right); "1" and "2" indicate anterior and posterior positions, respectively.

Toxicokinetics: blood samples were collected from all dogs prior to dosing and at 45 min, 2, 4, 6,

and 12 hrs postdosing in Day 1, and ≈23 hrs after patch application on Days 1, 21, 49, 77, 105, 133, 161, 189, 217, and 245, and prior to dosing and at 45 min, 2, 4, 6, 12, and 24 hrs after patch application on Day 272. Additional blood samples were collected from recovery animals following removal of the last patch (Day 274). Plasma samples were shipped to [redacted] for analysis of selegiline and metabolites. Selected worn patches were retained for possible analysis, but were discarded without analysis.

Results

Mortality: there were no unscheduled deaths during the study.

Clinical signs: the sponsor considered there to be no drug-related clinical signs. Of note, however, were the slightly increased incidence and/or no. of affected animals exhibiting no/few feces (M, F), and an increase in post-dose vomiting in HDF. Data on the incidence of patch reapplication/destruction and detection of patch(es) in feces are summarized in the following table (data are expressed as incidence/animals affected):

SIGN	MALES				FEMALES			
	CP	LD	MD	HD	CP	LD	MD	HD
patch reapplied	93/6	31/6	16/6	30/6	98/5	10/5	19/5	13/4
patch destroyed	108/6	64/6	90/6	85/6	115/6	64/6	77/6	87/6
patch detected in feces	81/5	11/3	10/3	75/6	21/5	5/3	21/4	9/4
patch off (at wrap)	7/3	1/1	9/4	0/0	3/3	4/3	11/6	6/4

[Note: the sponsor did a poor job summarizing the "patch" items, such as replacement of patch. Findings were broken into numerous subdivisions, making it very difficult to determine the important finding: was the patch on or off? (A similar approach was used in summarizing these findings in the chronic t.d. study in rat.) Also, the sponsor listed the incidences of "patch detected in feces (or fecal material)" in two different places, i.e., under "Excreta" and under "Other". The data under neither heading reflected the total incidence of this finding.]

Dermal irritation (i.e., edema, erythema, eschar, desquamation) was noted in all treatment grps and the placebo control. The severity and incidence of these findings were either fairly similar among groups or not consistently greater in treated grps, depending on the finding. There was still evidence of irritation in recovery animals, although signs were limited to red raised area at the application site, desquamation, and single incidence of slight eschar in the placebo control and HDF grps.

Body weights: the primary effect observed was an increase in mean body wt in untreated C grps compared to placebo control (CP) in both males and females, but particularly in females. In untreated CF, mean body wt was significantly increased from Day 42 to Day 112 (16-27%). In treated grps, body wt was not significantly affected compared to CP. In males, mean body wt tended to be lower in treated grps; however, there was no consistent dose-related pattern. Final mean body wts were reduced by 14, 3, and 11% in LDM, MDM, and HDM, respectively, compared to CPM. In females, final mean body wts were increased (compared to CPF) by 22, 3, and 14% in untreated CF, LDF, and MDF, respectively; at the HD, final mean body wt was similar to that in CPF. In recovery animals, final mean body wt was reduced by 4, 20, 5, and 23% in untreated CM, LDM, MDM, and HDM, respectively, and by 11% in HDF compared to CP grps. Final mean body wt was increased in untreated CF (38%) compared to CPF, but similar among the CPF, LDF, and MDF grps.

There were no consistent differences in mean body wt gain among grps in either males or females (main-study or recovery).

Food consumption: food intake was increased (10-40% in M, 11-33% in F) in untreated C grps compared to CP grps during the first 3 months, and sporadically thereafter. Also, in males, food intake was significantly increased in treated grps; however, the effect was

not consistent or not consistently dose-related. In females, food intake was generally similar among the CP and treated grps during the dosing period. No differences in food intake were noted in recovery animals.

Ophthalmoscopy: according to the veterinary ophthalmologist, Dr. ——, there were no drug-related findings.

ECG: numerical data for ECG parameters and hr were not provided, either in summary form or for individual animals. According to —— DVM, PhD, DACVIM, there were no drug-related effects. Individual data were provided for SAP and DAP; however, these data were not summarized.

Hematology: there were no clear drug-related effects. In males, there was a tendency for rbc parameters (ct, hgb, hct; 6-9%), wbc and segmented neutrophil cts (19-23%) to be slightly reduced, and for platelet ct to be slightly increased (24-35%) at the HD compared to CPM. In recovery HDM, platelet ct was slightly elevated (19%) and wbc and segmented neutrophil cts were slightly reduced (32-35%) compared to CPM-R. None of these differences was statistically significant. In females, there were transient (Day 89/90) decreases in rbc ct, hgb, and hct [14, 13, and 13%, respectively] compared to values for CPF; there were no differences among grps during the recovery period.

Clinical chemistry: in males, the only notable potentially drug-related effect was an increase in ALT throughout the dosing period in HDM. An examination of the individual data indicated that 3/6 HDM were affected. In HDM #325, ALT was elevated throughout the dosing period [70-160% compared to the high value in CPM]. In HDM #321, ALT was elevated [70-160%] at all but the last sampling time. In HDM #345, ALT was elevated [130-180%] on Days 33/34 and 89/90], only slightly elevated [20%] on Day 180/181, and elevated by 70% on Day 274/276. In untreated CM, urea N and cholesterol were significantly increased [31-57%] compared to CPM

In females, as in males, the only notable potentially drug-related finding was an increase in ALT. Mean ALT was increased in HDF throughout the dosing period (except on Day 33/34), however, the effect was small [30-61%] and not statistically significant. An examination of individual data indicated that 2/6 HDF were affected in HDF #359, ALT was elevated by 50-57% throughout the dosing period (except on Day 33/34). However, in HDF #374, there was a progressive increase in ALT [60% on Day 89/90, 80% on Day 180/181, and 140% on Day 274/276]; this animal was not followed during the recovery period. Mean GGT was transiently elevated in MDF and HDF on Day 89/90 [46-49%]; however, the effect was due both to a decrease in GGT in CPF (≈30% from baseline) and a slight increase in GGT in HDF. There did not appear to be any differences among grps during the recovery period.

Urinalysis: there were no clear drug-related effects. In males, urinary volume was increased in all grps relative to CPM on Days 33/34 [73, 29, 82, and 86% in untreated CM, LDM, MDM, and HDM, respectively] and 89/90 [150, 160, 76, and 110% in untreated CM, LDM, MDM, and HDM, respectively]. Urinary pH was increased in all treated grps relative to CPM on Day 33/34 [0.6, 0.6, 0.9 and 1.2 pH units in untreated CM, LDM, MDM, and HDM, respectively]. In females, there were no consistent, dose-related effects. [Summary data were provided only for urinary volume, pH, and specific gravity.]

Organ Weights: the following observations were notable, although not necessarily indicative of a drug-related effect: (a) increased adrenal wt in HDM #340 (34% compared to high CPM value); relative wt was not affected. Adrenal wt (absolute-relative) was also increased in HDF [mean: 32% compared to highest absolute wt in CPF; in HDF # 362: 16-7%, HDF #363: 53-30%; HDF #374: 22-65%]. (b) decreased absolute and relative prostate wt in HDM #325 [75-67%], (c) decreased absolute pituitary wt at all doses in males [22, 25,

and 25% at LD, MD, and HD, respectively] relative to CPM at the end of the recovery period. (d) absolute and relative uterus wt was reduced at all doses [42-55%; decrease in means was not dose-related]; at the HD, uterus wt was reduced in 3/4 females [70-73, 43-55, and 36-18% in HDF # 362, 363, and 374, respectively]. There were no notable findings in recovery females, although the small "n" made it difficult to evaluate the recovery data.

Gross pathology: there were few findings. In males, the only notable finding was a slight increase in the incidence of skin scabbing in HDM, both at the end of the main study [0/4 CPM, 1/4 untreated CM, 1/4 LDM, 1/4 MDM, and 2/4 HDM] and the recovery period [0/2 CPM, 0/2 untreated CM, 0/2 LDM, 0/2 MDM, 2/2 HDM]. In females, the incidence of enlarged axillary lymph node was increased at the HD at the end of the dosing period [1/4 CMF, 0/4 untreated CF, 1/4 LDF, 1/4 MDM, and 3/4 HDF]. There were no notable findings in recovery animals.

Histopathology: there were no apparent drug-related findings. Evidence of local irritation were noted in CP grps and all drug-treated grps. Local findings in main-study animals are summarized in the table below (pg 44). There were no clear drug-related local effects. Hyperplasia and/or inflammation were observed at the application site in CP and treated animals. With some exceptions, findings (e.g., hyperplasia) tended to be more severe in treated animals; however, in these cases, there was no clear, consistent dose-response. Tissues were not examined in recovery animals.

TK: the data were summarized in the sponsor's tables on pg 45.

TREATED SKIN SITE	FINDING	MALES				FEMALES			
		CP	LD	MD	HD	CP	LD	MD	HD
1L	hyperkeratosis								
	minimal	0/4	0/4	0/4	0/4	0/4	0/4	1/4	0/4
	hyperplasia								
	minimal	4/4	2/4	3/4	2/4	1/4	3/4	3/4	1/4
	mild	0/4	0/4	1/4	1/4	0/4	0/4	0/4	2/4
	acute inflammation								
	mild	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
	chronic inflammation								
	minimal	1/4	1/4	0/4	1/4	1/4	1/4	1/4	0/4
	mild	0/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4
	chronic/active inflammation								
	minimal	1/4	1/4	1/4	0/4	0/4	0/4	0/4	1/4
	mild	0/4	0/4	1/4	0/4	0/4	0/4	1/4	0/4
	vacuolar change								
	minimal	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
1R	hyperplasia								
	minimal	4/4	2/4	0/4	1/4	2/4	2/4	2/4	1/4
	mild	0/4	1/4	2/4	1/4	0/4	0/4	0/4	1/4
	moderate	0/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4
	acute inflammation								
	minimal	0/4	0/4	0/4	0/4	1/4	0/4	0/4	0/4
	mild	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
	chronic inflammation								
	minimal	1/4	3/4	2/4	1/4	0/4	0/4	0/4	1/4
	mild	0/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4
	chronic/active inflammation								
	minimal	2/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	mild	0/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4
	moderate	0/4	0/4	0/4	0/4	1/4	0/4	0/4	0/4
	vacuolar change								
	minimal	0/4	0/4	0/4	0/4	0/4	1/4	0/4	0/4
2L	hyperplasia								
	minimal	3/4	1/4	3/4	1/4	3/4	2/4	2/4	3/4
	mild	0/4	0/4	0/4	1/4	0/4	1/4	0/4	0/4
	moderate	0/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4
	acute inflammation								
	minimal	0/4	0/4	0/4	1/4	1/4	0/4	0/4	0/4
	mild	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
	chronic inflammation								
	minimal	2/4	0/4	1/4	1/4	0/4	1/4	1/4	1/4
	mild	0/4	0/4	0/4	1/4	1/4	0/4	0/4	0/4
	chronic/active inflammation								
	mild	0/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4
	vacuolar change								
	minimal	0/4	0/4	0/4	0/4	0/4	1/4	0/4	1/4
2R	hyperplasia								
	minimal	2/4	0/4	2/4	2/4	3/4	0/4	2/4	1/4
	mild	1/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
	moderate	0/4	0/4	1/4	1/4	0/4	0/4	0/4	0/4
	acute inflammation								
	minimal	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
	mild	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
	chronic inflammation								
	minimal	1/4	0/4	1/4	1/4	1/4	0/4	1/4	0/4
	mild	0/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4
	chronic/active inflammation								
	minimal	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	mild	0/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4
	vacuolar change								
	minimal	0/4	0/4	0/4	0/4	0/4	1/4	0/4	0/4

Toxicokinetics: the data are summarized in the following sponsor's table:

Table 1. Mean ± SD plasma concentrations of selegiline and its metabolites 23 hours after application of STS on selected dosing days

	Mean ± SD Analyte Concentration (ng/mL) 23 hr post dose Days 21-245							
	Selegiline		N-Desmethylselegiline		Amphetamine		Methamphetamine	
Dosage Level	M	F	M	F	M	F	M	F
6 mg/kg/day	6.63 ± 3.86	4.42 ± 2.59	1.69 ± 0.77	1.63 ± 0.88	22.0 ± 9.7	17.5 ± 8.4	5.22 ± 2.23	4.16 ± 2.34
Metabolite/ Selegiline Ratio	1	1	0.25	0.37	3.32	3.96	0.79	0.94
12 mg/kg/day	13.2 ± 6.4	12.3 ± 4.4	3.16 ± 1.18	2.94 ± 0.75	52.2 ± 23.6	48.2 ± 18.1	11.9 ± 5.1	10.8 ± 4.3
Metabolite/ Selegiline Ratio	1	1	0.24	0.24	3.95	3.92	0.90	0.88
24 mg/kg/day	28.3 ± 13.0	24.8 ± 12.0	3.93 ± 1.37	3.72 ± 1.25	90.8 ± 46.5	81.0 ± 31.6	18.3 ± 7.7	15.6 ± 6.4
Metabolite/ Selegiline Ratio	1	1	0.14	0.15	3.21	3.27	0.65	0.63

Table 2. Pharmacokinetic parameters of selegiline and its metabolites on Day 273

Pharmacokinetic Parameter & Dose	Analyte Mean ± SD (N=12) Parameter Value Day 273 (Male and Female Combined)			
	Selegiline	N-Desmethylselegiline	Amphetamine	Methamphetamine
6 mg/kg/day				
Cmax ng/mL	5.24 ± 3.32	1.96 ± 0.88	19.4 ± 8.8	4.36 ± 1.97
Tmax hr	6.33 ± 6.37	7.73 ± 8.24	8.56 ± 5.88	6.06 ± 6.55
AUC(0-24) ng•hr/mL	79.4 ± 38.6	30.3 ± 14.4	334 ± 154	74.8 ± 31.9
Css ng/mL	3.31 ± 1.61	1.26 ± 0.60	13.9 ± 6.4	3.12 ± 1.33
Metabolite/ Selegiline Ratio	1	0.38	4.20	0.94
12 mg/kg/day				
Cmax ng/mL	18.1 ± 7.5	4.77 ± 1.33	67.1 ± 23.8	16.0 ± 7.2
Tmax hr	8.67 ± 7.97	9.50 ± 8.91	6.50 ± 4.01	10.5 ± 6.8
AUC(0-24) ng•hr/mL	337 ± 97	93.0 ± 21.0	1296 ± 488	314 ± 135
Css ng/mL	14.1 ± 4.0	3.88 ± 0.87	54.0 ± 20.3	13.1 ± 5.6
Metabolite/ Selegiline Ratio	1	0.27	3.83	0.93
24 mg/kg/day				
Cmax ng/mL	42.7 ± 30.0	6.15 ± 2.81	116 ± 63	29.6 ± 25.2
Tmax hr	6.17 ± 6.24	9.00 ± 7.60	7.23 ± 6.39	6.50 ± 4.01
AUC(0-24) ng•hr/mL	712 ± 507	112 ± 55	2247 ± 1331	514 ± 363
Css ng/mL	29.7 ± 21.1	4.67 ± 2.31	93.6 ± 55.4	21.4 ± 70.6
Metabolite/ Selegiline Ratio	1	0.16	3.15	0.72

Toxicology summary and conclusions: the sponsor conducted chronic transdermal studies in Sprague-Dawley rat [6-mo] and Beagle dog [9-mo]. [Doses for the rat study were based, in part, on the results of a 21-day selegiline STS dose-range finding study.]

In the rat study, selegiline STS was administered to 20/sex/grp at doses of 0[placebo patch, CP], 0 [untreated, CU], 30, 60, and 120 mg/kg; patches were replaced daily. An additional 5/sex/grp were followed during a 1-mo recovery period. Observations included clinical signs, body wt, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, and terminal studies [gross pathology, organ wt, histopathology]; TK data were collected in satellite animals. [Clinical pathology

parameters were assessed in a subset of animals (i.e., 10/sex/grp).] Administered doses were calculated to be ≈20-40 mg/kg (LD), ≈50-70 mg/kg (MD), and ≈105-135 mg/kg (HD). Patches were retained in order to determine residual drug concentration; however, analyses were not conducted and retained patches were discarded. According to the report of a PK study in rat [Study APK-50-98B], the actual dose estimated to have been delivered following application of a 120-mg/kg dose was 24-25 mg/kg. [The plasma exposure values from the PK and 6-mo studies were quite comparable.] Therefore, the actual delivered doses were in all probability notably lower than the administered doses.

There were no drug-related deaths. The primary drug-related clinical signs consisted of aggressiveness [primarily HD, but observed only in treated animals] and an increased incidence of urine stains [primarily HD], dark material around the nose and/or mouth [all doses in males, HDF], tremors [HD], wobbly gait [MDF, HD], and vocalization [HDF]. Patches had to be reapplied or were destroyed in a majority of animals (including CP) at some time during the dosing period. In males, patches were either reapplied or destroyed [suggesting some decrease in dosing] on >10% of total days of dosing in only 1 HDM. However, in females, the number of animals was greater, particularly at the MD and HD, i.e., a total of 3, 2, 5, and 7 CP, LD, MD, and HD main-study females. [In addition to problems with the patch, dosing was not performed on 3 scheduled days due to "inclement weather".] To what extent dosing was compromised is impossible to determine. It does appear, however, that HDF may have been particularly affected. One ameliorating factor was that blood samples were collected for TK analysis at a number of sampling times during the dosing period; therefore, plasma data were probably helpful in estimating steady-state exposure.

Signs of local irritation were noted in all grps receiving patches, including CP grps, indicating that the patch itself was irritating. In addition, the incidence and/or severity of signs [erythema, eschar, desquamation] were increased at the HD, indicating that selegiline itself is irritating. Histopathological changes at the application site are consistent with these observations. The primary drug-related finding was epidermal hyperplasia, with both the incidence and severity being drug-related [HDM, LDF, MDF, HDF]. Local changes, both visual and microscopic, were reversible after 1 month of non-treatment.

Body wt was notably reduced in CPM and CPF, indicating that patch administration alone affected growth. Compared to CP grps, mean body wt was reduced in HDM, and to a lesser extent in HDF. Mean body wt was transiently reduced in MD grps. Mean body wt gain was not consistently affected in males, but was reduced in all treated grps in females. Changes in food intake were not entirely consistent with those in body wt, although mean food intake was reduced in HDM throughout most of the dosing period. There were no drug-related effects on clinical pathology parameters, except for a decrease in urinary volume [all doses, males and females; not clearly dose-related]. No drug-related ophthalmology findings were detected; however, there was an unusually high incidence of dacryoadenitis [i.e., inflammation of the lacrimal gland]; the veterinary ophthalmologist tentatively attributed this finding to the wrapping materials. The only apparent drug-related macroscopic findings were fur/hairloss (HD) and skin scabs (LDF, MD, HD). Small/soft testes was reported in 1/20 HDM; marked tubular atrophy and aspermatogenesis were detected upon microscopic examination. Liver wt (absolute and body-wt corrected) was increased at all doses in main-study females, and in HD recovery females; however, there were no microscopic correlates. The primary microscopic findings were detected at the application site, as discussed above. The only other drug-related finding was an increase in the severity of dilatation of the uterus in HDF (uterine wt was not affected). Whether this represents differences in physiological status or a drug-related effect (similar to estrogens) is unclear; the sponsor did not consider it a drug-related finding.

The data from the 6-mo study indicate that the only potentially dose-limiting drug effect was a decrease in body wt. Although the drug effect on body wt did not exceed 10%, the drug-effect in combination with the "patch effect" resulted in decreases in body wt (compared to untreated Cs) of >30% at the HD. Also,

CNS signs were observed in a few HD animals. Therefore, the doses were probably adequate. [Although the dose-range finding study was conducted at higher doses (up to 160 mg/kg), the data were not helpful in determining an MTD.] The primary drug-related effects were observed at the application site. Although the epidermal hyperplasia was reversible, it is still notable that both the patch alone and selegiline STS were irritating and that the incidence and severity of epidermal hyperplasia was dose-related (i.e., no no-effect level). This raises the issue of the potential for a carcinogenic effect at the application site. [The mouse and rat carcinogenicity studies submitted in support of the STS formulation were conducted using the oral route.]

TK data were collected on Days 1 and 182 of dosing. At all doses, plasma levels of selegiline were higher than those of metabolites, N-desmethylselegiline, amphetamine, and methamphetamine. Plasma exposure for selegiline and metabolites increased in a fairly linear manner with dose. The one gender difference was an increase in the extent of metabolism to methamphetamine (≈75-170%), and to a lesser extent, amphetamine (40-140%) in females as compared to males.

In the dog study, selegiline STS was administered to 4/sex/grp at doses of 0 [placebo patch, CP], 0 [untreated, CU], 6, 12, and 24 mg/kg/day; patches were replaced daily. The HD was the highest feasible dose. [The amount of drug actually delivered was not quantitated. However, in a separate PK study conducted in dog at 6 and 24 mg/kg, residual drug in the patches was quantitated and actual delivered doses were determined to be 0.68 ± 0.08 - 0.86 ± 0.22 mg/kg/day at the LD (6 mg/kg) and 2.91 ± 0.56 - 3.27 ± 0.51 mg/kg/day at the HD (24 mg/kg). A comparison of plasma exposure data between these studies indicated similar exposure (C_{max}, AUC) at the LD, but 20-100% higher exposure in the PK study at the HD. This would suggest a slightly lower delivered HD in the 9-mo study compared to the PK study.] An additional 2/sex/grp were followed during a 1-mo recovery period. Observations included clinical signs, body wt, food consumption, ophthalmology, ECG, hematology, clinical chemistry, and terminal studies [gross pathology, organ wt, histopathology]; TK data were collected at numerous time points during the dosing period, and at the end of the recovery period in recovery animals.

There were no unscheduled deaths and no drug-related clinical signs observed during the study. As in the rat study, there were problems with keeping the patch in place in all grps. Patches had to be reapplied or destroyed in all animals (receiving a patch) at some time during the dosing period. [Therefore, as for rat, the plasma exposure data provide the only fairly reliable estimate of dosing.] Dermal irritation was evident in all grps receiving patches; there were no clear drug-related effects; evidence of irritation was still noted in HDF-R (recovery females). Mean body wt was reduced in CP grps as compared to CU grps, indicating an effect of patch application alone. There were no clear drug-related body wt effects in main-study animals. Food intake was reduced in CP as compared to CU grps, consistent with body wt effects; no additional dose-related effect was noted. There were no clear drug-related effects on ophthalmology, ECG [no data provided], hematology, or urinalysis parameters. The one clinical chemistry finding was an increase in ALT in HDM and HDF. Liver wt was not affected and there were no microscopic correlates detected in liver. The only notable gross findings were an increased incidence of skin scabs in HDM (main-study and recovery) and enlarged axillary lymph nodes in HDF (main-study). Organ wts were not clearly affected by drug, and no drug-related microscopic findings were detected. The primary microscopic finding of note was local irritation; however, microscopic changes [inflammation, epidermal hyperplasia] were fairly similar in C and treated grps. The severity of epidermal hyperplasia tended to be greater in a few treated animals; however, no consistent dose-related pattern was observed. TK data indicated systemic exposure to selegiline and metabolites, N-desmethylselegiline, amphetamine, and methamphetamine. The major circulating drug-related substance was amphetamine [3-4 fold higher than the parent based on AUC]. Plasma exposure (C_{max}, AUC) to selegiline increased in a greater-than dose proportionate manner between the LD and MD, and then in a fairly dose-proportionate manner between the MD and HD.

The sponsor provided summary plasma exposure data from 9 clinical trials. The mean (range) AUCs (ng•hr/mL) for selegiline and metabolites following multiple doses (7-11 days) of the 20 mg/20 cm^2 patch are as follows:

selegiline	N-desmethylselegiline	amphetamine	methamphetamine
66.1 (49.5-80.4)	35.3 (30.9-43.9)	60.9 (43.4-76.1)	147 (85.4-203)

Plasma AUCs (at steady-state) for selegiline at the HDs used in the rat and dog studies were 34- and 11-fold higher than the plasma AUC in humans following the clinical dose. Although no serious drug-related toxicities were observed at the HD, the MD could be considered a NOAEL due to increases in ALT and some clinical signs at the HD.

Oral studies: chronic oral toxicity studies were submitted to NDA 19-334 for oral selegiline. These consisted of 6-mo gavage studies in Long-Evans [0, 5, 15, 30 mg/kg] and Sprague-Dawley [0, 10, 30, 90 mg/kg] rats, a 1-yr dietary study in Sprague-Dawley rat [0, 0.7, 3.5, 17.5 mg/kg], two 6-mo oral studies [0, 5, 10, 20 mg/kg; 0, 3, 10, 30 mg/kg] and a 1-yr oral toxicity study in Beagle dog [0, 1, 4, 16 mg/kg].

Minimal effects [slight reduction in body wt] were observed in the study in Long-Evans rat. In Sprague-Dawley rat, there was an increase in mortality at 30-90 mg/kg, clinical signs (including clonic seizures) at 90 mg/kg, and decreased body wt gain in males. An increase in pulmonary edema was observed at 30 and 90 mg/kg; pulmonary edema was determined to be the cause of death in several HDM. No drug-related microscopic changes were evident. In the 1-yr study conducted at lower doses, increased excitability was observed at 17.5 mg/kg and adverse effects on body wt were observed at 3.5 and 17.5 mg/kg; no other drug-related findings were observed.

No drug-related effects were observed in the 6-mo dog study conducted at doses of 5-20 mg/kg. In the 2^{nd} 6-mo study, clinical signs [decreases in spontaneous motor activity, mydriasis, pacing/turning, and/or continuous salivation] were observed at all doses. Body wt loss was observed at 30 mg/kg, while decreases in body wt gain were observed at the lower doses. Histopathology findings consisted of aspermatogenesis and fibrosis of the prostate in 1 dog at 30 mg/kg, and thymic atrophy was detected in all animals treated at 30 mg/kg. In the 1-yr study, clinical signs [increased spontaneous motor activity, salivation] and decreases in body wt gain were observed at 4 and 16 mg/kg. Histopathology findings consisted of an increase in foci of hemosiderin deposition in macrophages and/or Kupffer cells, spleen lymphoid atrophy, and thymic involution at 16 mg/kg. Hemosiderin deposition was also observed at the lower doses.

Adverse effects on body wt was the primary drug-related effect observed in both the oral and transdermal studies. The prostate findings, noted in a single dog, are notable only considering the effects observed in rat in the STS studies. The mortality and clinical signs observed with oral dosing may be due to metabolites since plasma levels of metabolites are higher (relative to parent) following oral compared to transdermal dosing. TK data were not collected in the oral toxicity studies.

V. CARCINOGENICITY

Background: in the original NDA for oral selegiline [approved, 1989], carcinogenicity studies were not required for approval, but were considered a Phase 4 commitment. Carcinogenicity studies in mouse (78-wk) and rat (104-wk) were submitted in NDA 20-647 for a new oral formulation of selegiline. These studies were reviewed [Review and Evaluation of Pharmacology and Toxicology Data, Lois M. Freed, Ph.D., 3/19/96], but were considered to be inadequate due to the lack of microscopic data for the LD and MD grps in both the mouse and rat studies. There was concern that the C and HD data alone provided an insensitive assessment of carcinogenic risk because of the reduced body wt gain observed at the HD in both studies. The sponsor subsequently provided these data. A statistical evaluation was conducted on the original data, but has not been conducted on the full datasets for these studies.

There are two issues that need to be addressed: (1) are the oral carcinogenicity studies adequate and (2) are they adequate to support a transdermal formulation of selegiline. The sponsor was asked to address #2 by conducting TK bridging studies [Division letter, 1/18/00]. [Communications between the Division and the sponsor regarding the carcinogenicity studies are further discussed in the "Carcinogenicity summary and conclusions" section.] In response, the sponsor submitted a 14-day dietary PK bridging study in rats; no PK bridging study was submitted in mice.

1. Study Title: **A 14-day oral (dietary) pharmacokinetic study in rats with selegiline HCl** (Somerset Study No: TOX-549-00, Vol #1.046, Conducting laboratory and location: , , date of study initiation: 4/24/00, GLP, QA)

Methods

Dosing

species/strain: Sprague-Dawley rat [CD®(SD)1GS BR] [Note: the CD® (SD)GS BR-Cesarean-derived (Sprague-Dawley) barrier-raised rat was used in the 2-yr carcinogenicity; this strain was apparently no longer available.]

#/sex/group or time point: 65/sex

age: males were ≈9 wks old; females were ≈11 wks old at study initiation.

initial body weight: 281-332 gm for males, 214-279 gm for females.

housing: animals were housed individually.

satellite groups used for toxicokinetics or recovery: no

dosage groups in administered units: 17.5 mg/kg/day

route, form, volume, and infusion rate: dietary

duration: "...a minimum of 15 consecutive days"

Dose Justification: the dose used was the HD used in the 2-yr dietary carcinogenicity study in rat [IRI Project No. 435507]

Drug, lot#, and % purity: selegiline HCl, lot no. 9811025, purity not stated.

Formulation/vehicle: drug-diet admixture, prepared fresh on Days 1, 8, and 13 using [crude protein: ≥20.0%, crude fat: ≥4.5%, crude fiber ≤5.5%, ash: ≤7.0%, added minerals: ≤2.5%]. [Information was also provided for , it is unclear why.] Drug concentration was adjusted based on body wt and food consumption. Drug concentration [prior to start of dosing, during Wk 1 and at the end of the dosing period] and homogeneity were analyzed in triplicate. Drug stability in the admixture was determined after 0, 3, and 8/9 days of storage at room temperature.

Observations and times:

Clinical signs: animals were observed twice daily for general health, mortality, and morbidity. Clinical signs were recorded daily.

Body weights: animals were weighed prior to start of dosing, and on Days 1, 8, 13, 14, and 15

(5/sex only) of dosing.

Food consumption: food intake was recorded prior to start of dosing and on Days 1-8, 8-13, 13-14, 14-15, and 15-16 of dosing. Drug intake was measured during these same intervals only in 5/sex.

Toxicokinetics: blood samples were collected (via the orbital plexus) prior to start of the 12-hr dark cycle on Day 15 (≈1700 hrs), at 45 min, 2, 4, 6, 8, 10, and 12 hrs after the start of the dark cycle, at 1, 3, 6, and 9 hrs after the start of the 12-hr light cycle, and just prior to start of the dark cycle on Day 16. Five per sex were examined per sampling time. Plasma samples were frozen (-20° C) and shipped to [redacted] for analysis.

Deviations from protocol: (1) the sponsor stated that "With the exception of the males on Days 12 through 16, the dosage concentration was not maintained at a higher level in an attempt to deliver 17.5 mg/kg/day to the animals. The dosage levels were designed at concentrations based on exactly 17.5 mg/kg/day". (2) food intake intervals were not exactly 24 hrs: Day 13-14 was ≈19 hrs, Day 14-15 was ≈30 hrs. This didn't appear to affect mean food intake in males, but food intake in females (mean on Day 14-15) "...is remarkably increased compared to Day 13 to 14".

Results

Clinical signs: no drug-related clinical signs were observed.

Body weights: in males, mean body wt gain was noted throughout the dosing period; final mean body wt was 16% higher compared to the last baseline measurement. In females, body wt loss or minimal gain was noted in the majority of females. Final mean body wt was 4% lower than mean wt at baseline.

Food consumption: food intake was fairly stable throughout the dosing period in males. In females, food intake tended to be reduced, particularly during Days 1-8 and Days 13-14 [i.e., mean intake was 12-16 gm vs 10 gm at baseline and 18-20 gm on Days 14-5 and Days 15-16.

Drug intake: data on achieved doses were summarized in the following sponsor's table:

Mean Test Article Consumption (mg/kg/day)
Target Dose Level: 17.5 mg/kg/day

Interval	Males	Females
Days 1 to 8	15.2	13.5
Days 8 to 13	17.2	19.7
Days 13 to 14	17.0	12.7
Days 14 to 15	19.2	21.8
Mean	17.2	16.9
Range	15.2 - 19.2	12.7 - 21.8

Drug-diet admixture analyses: homogeneity was demonstrated [top: [redacted] ppm; middle: [redacted] ppm; bottom: [redacted] ppm]. Stability analyses were conducted on 5/9/00 and 5/21/00; actual concentrations were [redacted] of intended and were similar on both days of analysis.

Toxicokinetics: results provided in a separate report.

2. Study Title: **A 14-day oral (dietary) pharmacokinetic study in rats with selegiline HCl: Pharmacokinetic Evaluation** (Somerset Study No: TOX-549-00, Vol #1.047, Conducting laboratory and location: [redacted] PK evaluation: [redacted] date of study initiation: 4/24/00, GLP, QA).

Methods: the conduct of the in-life study, including blood sampling times for TK analysis, was provided previously [#1, this section]. [It was stated that blood samples were "normally" collected within 15-20 min of the scheduled time.] The sponsor noted in the Introduction to this report that chiral assays were not used in these analyses, but that a published report by Shin (1997) [Shin H-S. *Drug Met Disp* 25:657-662, 1997] "...would indicate that the three metabolites formed from selegiline would also be R-(-)-enantiomers". The report also notes two differences between the 14-day dietary study and the 2-yr dietary carcinogenicity study in rat: (a) different strains and (b) different diets; — was used in the 14-day study and — was used in the carciongenicity study. [The macronutrient ingredients for — was given previously [#1, this section]; the composition of the — diet was as follows: crude protein ≥14.0%, crude fat ≥2.5%, crude fiber ≤6.0%, ash ≤6.0%, added minerals ≤2.5%.]

Selegiline, N-desmethylselegiline, amphetamine, and methamphetamine were quantitated in plasma using a GC/MS system. The LLOQ was — ng/mL. It was noted that "Sufficient stability data were available in rat plasma from the time the samples were collected until the completion of the analyses". Methods validation data were provided in — Method Validation Report, Project Code AAVP.

Results: TK data are based on examination of blood samples collected from 5 different animals per sex at each sampling time, i.e., serial samples were not taken. The data are summarized in the following sponsor's table and figures:

Pharmacokinetic Parameter	Analyte Pharmacokinetic Parameter Value			
	Selegiline	N-Desmethylselegiline	Amphetamine	Methamphetamine
Male rats				
Cmax ng/mL	3.36	12.4	28.5	21.2
Tmax hr	24	12	12	12
AUC(0-24) ng•hr/mL	29.2	166	412	319
Css ng/mL	1.22	6.92	17.2	13.3
Metabolite/ Selegiline AUC Ratio	1	5.68	14.1	10.9
Female rats				
Cmax ng/mL	11.0	27.2	61.9	89.7
Tmax hr	10	10	12	12
AUC(0-24) ng•hr/mL	126	364	948	1315
Css ng/mL	5.25	15.2	39.5	54.8
Metabolite/ Selegiline AUC Ratio	1	2.89	7.52	10.4

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Figure 1a
Mean Plasma Concentration vs Time Profiles on Days 15/16
Following Oral Administration of Selegiline HCl as a Dietary Admixture to Male Rats
at 17.5 mg/kg/day (Targeted)

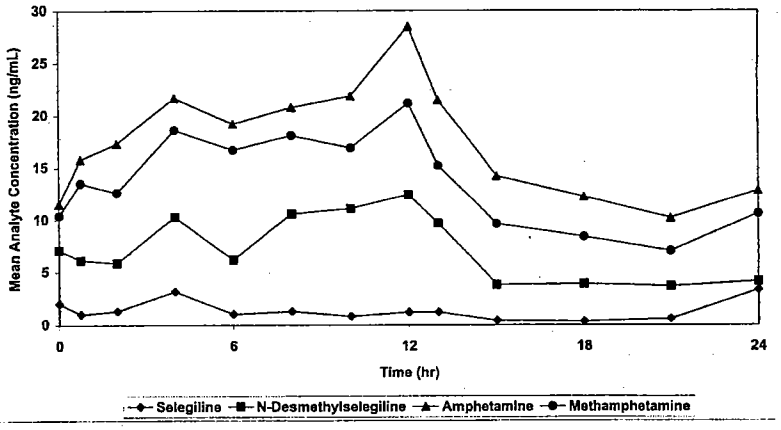
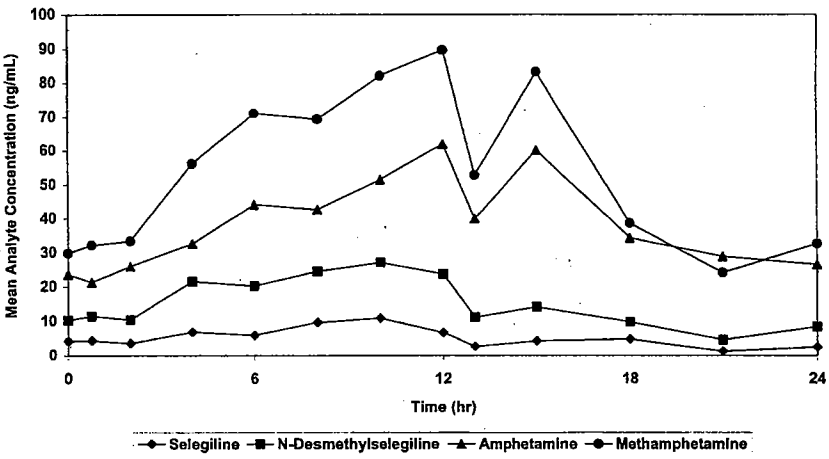


Figure 1b
Mean Plasma Concentration vs Time Profiles on Days 15/16
Following Oral Administration of Selegiline HCl as a Dietary Admixture to Female Rats
at 17.5 mg/kg/day (Targeted)



3. Study Title: **Selegiline hydrochloride. 78 week carcinogenicity study in mice with administration by diet: Histologic evaluation of tissues from the mouse carcinogenicity study** [⟶ Project No. 435664/453730. Supplement to NDA 20-647, 4/20/98, Vol #1-2 of 4, Conducting laboratory and location: ⟶ date of study initiation: 4/9/97, GLP.]

Methods: the purpose of this study was to provide microscopic data for the LD and MD grps of the 78-wk oral carcinogenicity study in CD-1 mice ⟶ Project No. 435664]. In that study, selegline HCl was administered as a drug-diet admixture at doses of 0, 3, 10, and 30 mg/kg/kg. Animals were housed individually. Diets were prepared weekly and drug concentrations were adjusted every 1-4 wks for change in body wt. Analysis of drug concentrations indicated that actual concentrations were within 30% of intended concentrations. One exception occurred at Wk 54 in females, a week during which the actual concentration was only ≈34% of intended. No TK data were provided in the original report. The following observations were performed: daily observation (clinical signs, palpable growths), body

wt/food consumption (prior to dosing, weekly during dosing until Wk 13, every 4 wks thereafter), differential blood counts (Wks 51 and 76 of dosing in C and HD animals), gross (all animals) and microscopic pathology [tissues examined: adrenal, abnormal tissue, bladder, bone (sternum), brain, heart, intestine (ileum, colon), kidney, liver/gall bladder, lungs (perfused), mammary gland, mesenteric lymph node, testes (with epididymides), thymus, thyroid (with parathyroid if present), trachea, esophagus, ovaries (with fallopian tubes), pancreas, pituitary, prostate, skin, spleen, stomach (glandular, nonglandular), submaxillary salivary gland, uterus]. [The following tissues (included in a complete battery) were not examined (except when a gross lesion was identified): duodenum, jejunum, cecum, rectum, eye, Harderian gland, lacrimal gland, larnyx, cervical or mandibular lymph nodes, nasal cavity, optic nerves, peripheral nerve (sciatic nerve), pharynx, seminal vesicles, skeletal muscle, spinal cord, vagina/cervix, Zymbal gland.] No organ/tissue wt data were collected.

In the original study submission, microscopic findings in all tissues examined were provided only for C and HD grps (also in animals dying prematurely). [Kidney, liver, and lung were examined in all grps.] The present study report provides microscopic data for the LD and MD grps, based on examination of the following tissues [4-6 μm sections stained with H & E]: gross lesions, adrenal, bone (sternum), brain, GI (esophagus, stomach, ileum, colon), heart, mammary gland, mesenteric lymph node, ovary, pancreas, pituitary, prostate, skin, spleen, submaxillary salivary gland, testis, thymus, thyroid/parathyroid, trachea, urinary bladder, uterus. All tissues for the entire study were peer reviewed; the peer review process included the following: (a) QA of the draft pathology report and pathology materials, (b) examination of all tissues from 10% of males and females in all grps [including C and HD grps], (c) examination of "...any target organs from all animals...[and]...of all neoplasms and hyperplasias". Statistical evaluations were conducted using Fisher's exact test (two-tailed).

Results [included are critical data from the original review that were not provided in this report].
Mortality: there were 67 unscheduled deaths during the study. The distribution of deaths among grps is provided in the following sponsor's table and Figs 1-2:

	Group/Dose Level (mg Selegiline Hydrochloride.kg^{-1}.day^{-1})			
Sex	1	2	3	4
	(0)	(3)	(10)	(30)
♂	5/50	12/50	9/50	7/50
♀	9/50	10/50	8/50	7/50

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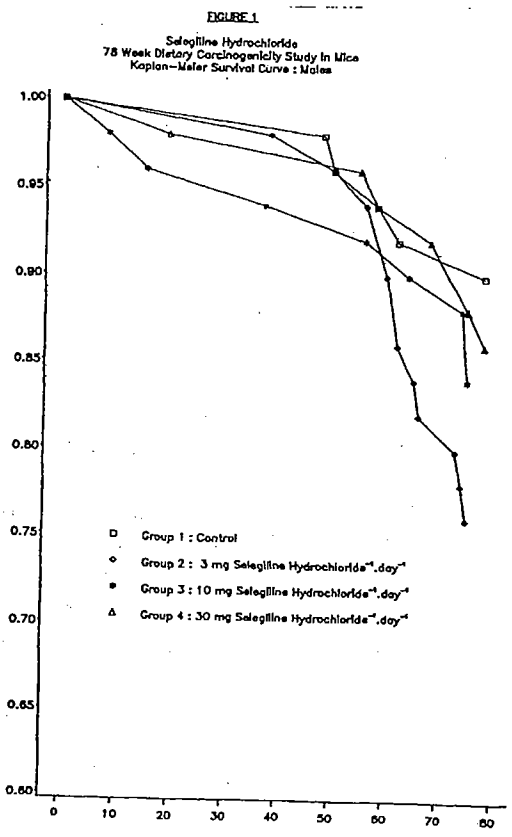

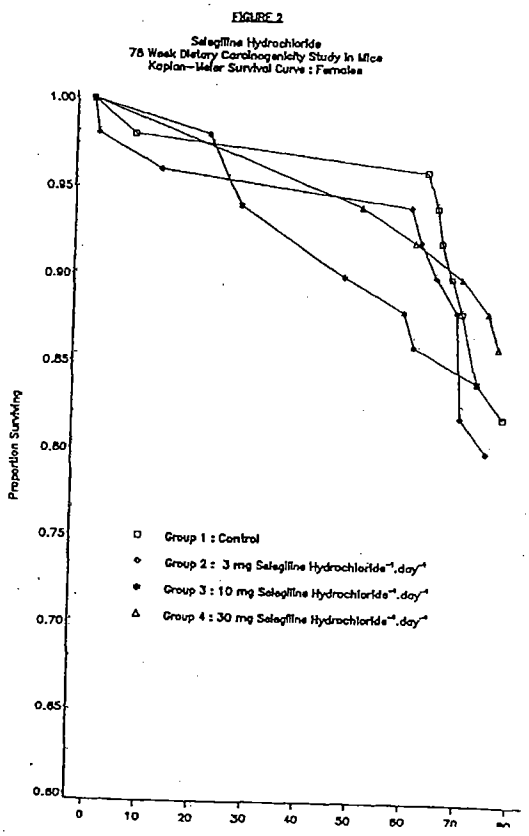

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Clinical signs: no drug-related clinical signs were observed.

Body wt: in males, reductions in body wt gain were noted at the MD and HD (27 and 48%, respectively). In terms of absolute body wt, final mean wts were reduced by 8 and 16% in MDM and HDM (as compared to CM). Drug effects were evident from Wk 4 on at the HD and from Wk 44 on at the MD.

In females, reductions in overall body wt gain were noted at all doses (15, 23, and 46% at LD, MD, and HD, respectively). In terms of absolute body wt, final mean wts were reduced by 7, 9, and 18%, respectively. Drug effects were evident from Wk 68 on at the LD, Wk 44 on at the MD, and from Wk 8 on at the HD.

Body wt effects are illustrated in the following sponsor's Fig 3-4:

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FIGURE 3

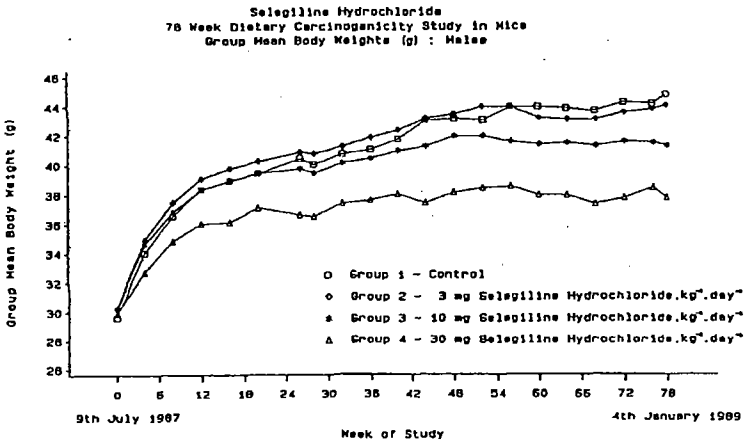
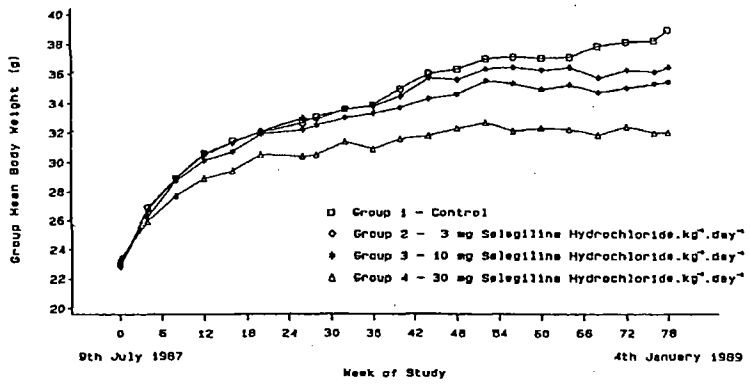


FIGURE 4



Food consumption: there were no drug-related effects on food intake. This would suggest either reduced efficiency of energy conversion at the MD and HD in males and at all doses in females or dose-related spillage (which was not reported as a drug-related clinical sign).

Gross pathology: no gross lesions were considered drug-related. No summary table was provided.

Histopathology: the only non-tumor finding considered drug-related by the sponsor was a reduced incidence of vacuolation of hepatocytes in MD and HD males. This was considered secondary to effects on body wt. It should be noted, however, that similar decreases in mean body wt (relative to C) were noted in treated females; however, no differences in the incidences of liver vacuolation were observed among grps. Selected non-tumor findings are summarized in the following table: