CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-641/S-008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	21-641
NDA type	Response to Phase 4 commitment
Submission Dates	Feb 06 2009
Submission Type	Study reports in response to Phase 4 commitment
Brand Name	Azilect®
Generic Name	**Rasagiline mesylate**
Reviewer	Hristina Dimova, PhD
Team Leader	Angela Men, MD, PhD
OCP Division	Clinical Pharmacology 1 (DCP1)
OND Division	Division of Neurology Drug Products
Sponsor	Teva NeuroSciences
Dosage Form; Strength	Tablet, 0.5 mg and 1 mg
Proposed Indication	Idiopathic Parkinson's disease
Proposed Dosage Regimen	Oral

1. Background

NDA for Azilect (rasagiline mesylate) was approved on May 16, 2006 for the treatment of early and advanced Parkinson's Disease. As part of the Phase 4 commitments listed in the approval letter, the sponsor committed to conduct a formal tyramine challenge study evaluation with multiple dose levels of rasagiline with positive control and selegiline comparator arms.
In addition, the sponsor provided proposed revisions to the labeling regarding selectivitiy for MAO-B and additional related changes.

2. Current Submission

This submission is a response to the post marketing (Phase 4) commitment, which contains the Final study reports for study TVP-1012-120 as well as study TVP-1012/TYR-400.
TVP-1012-120 is a phase 1, double blind, placebo controlled, randomized study to evaluate the interaction between orally administered tyramine hydrochloride and rasagiline mesylate in healthy subjects.
TVP-1012/TYR-400 is an open label, randomized, single dose, 3-way-crossover pilot study to assess the effect of food on the bioavailability of tyramine from a tyramine-rich meal.

2.1 TVP-1012-120

2.1.1 Study Title

A PHASE I, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED (WITHIN EACH GROUP) STUDY TO EVALUATE THE INTERACTION BETWEEN ORALLY ADMINISTERED TYRAMINE HYDROCHLORIDE AND RASAGILINE MESILATE IN HEALTHY SUBJECTS

2.1.2 Study Rationale

At the time of approval, the sponsor had not adequately characterized the potential of the drug to cause hypertensive "cheese" reaction. The approval letter provided an outline of important elements that should be incorporated into the study design of the formal tyramine challenge study:

- An appropriate number of subjects (e.g. approximately 20 per arm, equal number of males and females 40 to 70 years of age)
- An appropriate positive control
- The use of multiple dose levels of rasagiline
- The use of selegiline as an additional comparator
- The use of baseline pre-treatment tyramine doses of 25, 50, and 100 mg and dose increments above 100 mg of 100 mg up to 800 mg. Post treatment tyramine will use a similar dosing as pre-treatment, but starting doses will be lower. Tyramine doses will be administered on separate days.
- The use of blood pressure criterion of three consecutive systolic increases of at least 30 mm Hg with close monitoring at 5 minute intervals over at least 2 hours

and collection of at least 3 blood pressure measurements within 15-30 minutes prior to tyramine administration to serve as an integrated average blood pressure for comparison to a threshold pressor response after tyramine.

- Measurement of plasma tyramine at 30 minutes after each tyramine challenge study in all treatment groups.

2.1.3. TVP-1012-120 Synopsis

Study Design	Double-blind, placebo-controlled, randomized (within each group), positive and comparator control, multiple dose study in healthy subjects.
Study Population	N=149 Healthy subjects Age: 40-70 years Male to female ratio in Group 3: 39.1/60.9 Up to 15% smokers (CYP 1A2 is the major isoenzyme involved in rasagiline metabolism).
Treatment Group	Group 1: 45 mg/day phenelzine (positive control) Group 2: 10 mg/day selegiline (comparator) and matching placebo Group 3: 1 mg/day rasagiline and matching placebo Group 4a and 4b: 2 mg/day rasagiline and matching placebo Group 5: 4 mg/day rasagiline and matching placebo Group 6: 6 mg/day rasagiline and matching placebo
Dosage and Administration	All drugs were administered with 240 ml water. In Period 1 and in Period 3, no food was allowed from at least 10 hours before tyramine administration and until at least 4 h post-tyramine dose.
PK Sampling: Blood	Tyramine: Period 1, Days 3-10: Pre-dose, 5, 15, 30 min (and 60 min Part of Group 1 and Groups 3, 5 and 6 only) after tyramine administration Period 3, Days 25-35 or 41-51 (Group 4b): pre-dose, 35, 45, 60 and 90 (Part of Group 1 and Groups 3, 5 and 6 only) min after tyramine dosing Rasagiline: Group 4a, Day 23 and Group 4b, Day 39: Pre-dose and 15, 30, 45 min and 1, 1.5, 3, 4 h after rasagiline administration Groups 3, 5 and 6, Day 23: pre-dose and 15, 30, 45 min and 1, 1.5, 2, 3, 5, 8, 12, 16 and 24 h after rasagiline administration
PD sampling: blood DHPG (see p. 5)	Day 1: Before and 2 hours after tyramine administration Day 24 (or Day 40, group 4b): Before and 0.5 and 2.5 hours after tyramine administration
Analysis	Tyramine: liquid/liquid extraction at pH 8, followed by HPLC with fluorescence detection ; LOQ in plasma 0.5 ng/mL Rasagiline and metabolite 1-AI: liquid/liquid extraction at basic pH, dervatization with pentafluorobenzoylchlonde, followed by gas chromatagraphy with mass spectrometric detection. Rasagiline LOQ =0.25 ng/mL 1-AI LOQ = 0.5 ng/mL DHPG in human plasma treated with EDTA and metabisulfite. Purification by

	SPE, followed by HPLC with electrochemical detection. LOQ in plasma: 50 pg/mL
PK Assessment	C_{max}, T_{max}, $t_{½}$, AUC_t and AUC_{0-24} for Tyramine, Rasagiline and 1-AI
Safety Assessment	Vital signs, adverse events, laboratory tests, EKGs
PD Assessment	DHPG plasma concentrations and descriptive statistics by treatment group and time point (results for Groups 4a and 4b presented both separately and pooled).

Objectives:

- To assess tyramine sensitivity when administered with rasagiline, and the selectivity of rasagiline for monoamine oxidase type B (MAO-B)
- To investigate orthostatic blood pressure (BP) and pulse timed to rasagiline dosing

- Period 1

All subjects received ascending dose levels of tyramine on Days 1-10:

Administration of Tyramine in Period 1

Day	1	2	3	4	5	6	7	8	9	10
Total dose (mg)	25	50	100	200	300	400	500	600	700	800
No. of units x strength (mg)	1x25	2x25	1x100	2x100	3x100	4x100	5x100	6x100	7x100	8x100

Only subjects who presented an increase of at least 30 mmHg from baseline in three consecutive readings within 4 h after their last tyramine dose on day 10 were included in Periods 2 and 3.

- Period 2

Group 1: 15 mg phenelzine t.i.d. for 14 days (Days 11-24)
Group 2: 5 mg selegiline b.i.d. for 14 days (Days 11-24)
Group 3: 1 mg rasagiline or placebo, o.d. for 14 days (Days 11-24)
Group 4a: 2 mg rasagiline or placebo o.d. for 14 days (Days 11-24)
Group 4b: 2 mg rasagiline or placebo o.d. for 30 days (Days 11-40)
Group 5: 4 mg rasagiline or placebo, o.d. for 14 days (Days 11-24)
Group 6: 6 mg rasagiline or placebo, o.d. for 14 days (Days 11-24)

- Period 3

In Period 3 subjects received the same treatment as they received in Period 2, co-administered with escalating doses of tyramine:

Administration of Tyramine in Period 3, Group 1

Day	25	26	27	28	29	30	31	32	33	34	35
Total dose (mg)	5	15	25	35	45	55	65	75	85	95	105
No. of Units x strength (mg)	1x5	3x5	1x25	1x25 + 2x5	1x25 + 4x5	2x25 + 1x5	2x25 + 3x5	3x25	3x25 + 2x5	3x25 + 4x5	1x100 +1x5

Administration of Tyramine in Period 3, Groups 2 to 6

Day	25	26	27	28	29	30	31	32	33	34	35
Day *	41	42	43	44	45	46	47	48	49	50	51
Total dose (mg)	12.5	25	50	100	200	300	400	500	600	700	800
No. of Units x strength (mg)	1x 12.5	1x 25	2x 25	1x 100	2x 100	3x 100	4x 100	5x 100	6x 100	7x 100	8x 100

* for Group 4b only

2.1.4. TVP-1012-120 Results

Sample analysis

Analytical method for tyramine in human plasma

The analytical assay involved a liquid/liquid extraction at pH 8 and back-extraction at acid pH followed by reversed phase liquid chromatography (column Symmetry Shield C18) with fluorescence detection. The method was shown to be linear from 0.500 to 50.0 ng/mL. While analytical method for tyramine in human plasma was successfully validated, its performance during the analysis of the study samples was unsatisfactory. The selectivity of the analytical method was poor, resulting in some cases the software system integrating a chromatographic peak at a retention time close to the retention time of tyramine which represented more than 20% of the LLOQ. The consequence was that a chromatographic peak was detected in double blank and in blank samples. Also, the baseline was not stable (see Figure 1), further complicating the integration of the peaks and the interpretation of the results.

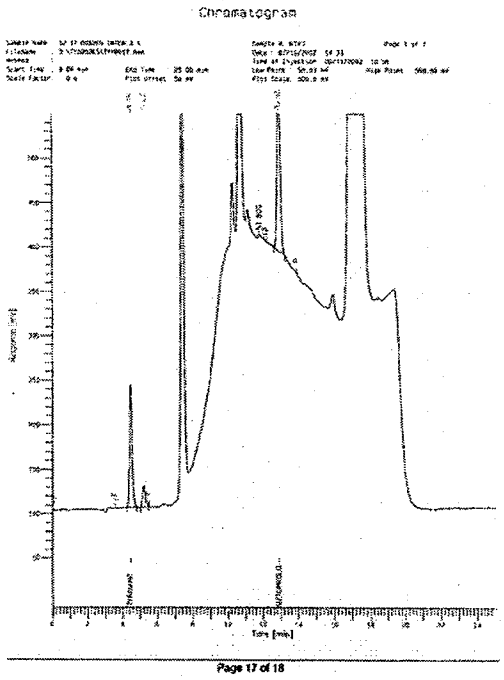

Figure 1: Representative chromatogram for tyramine in human plasma

The problems with the analytical method for tyramine resulted in high percentage (36%) of failed runs/batches. This, coupled with the large number of missing samples for different time points/subjects, makes the results for tyramine not interpretable. Some examples are shown in Figure 2 to demonstrate this point.

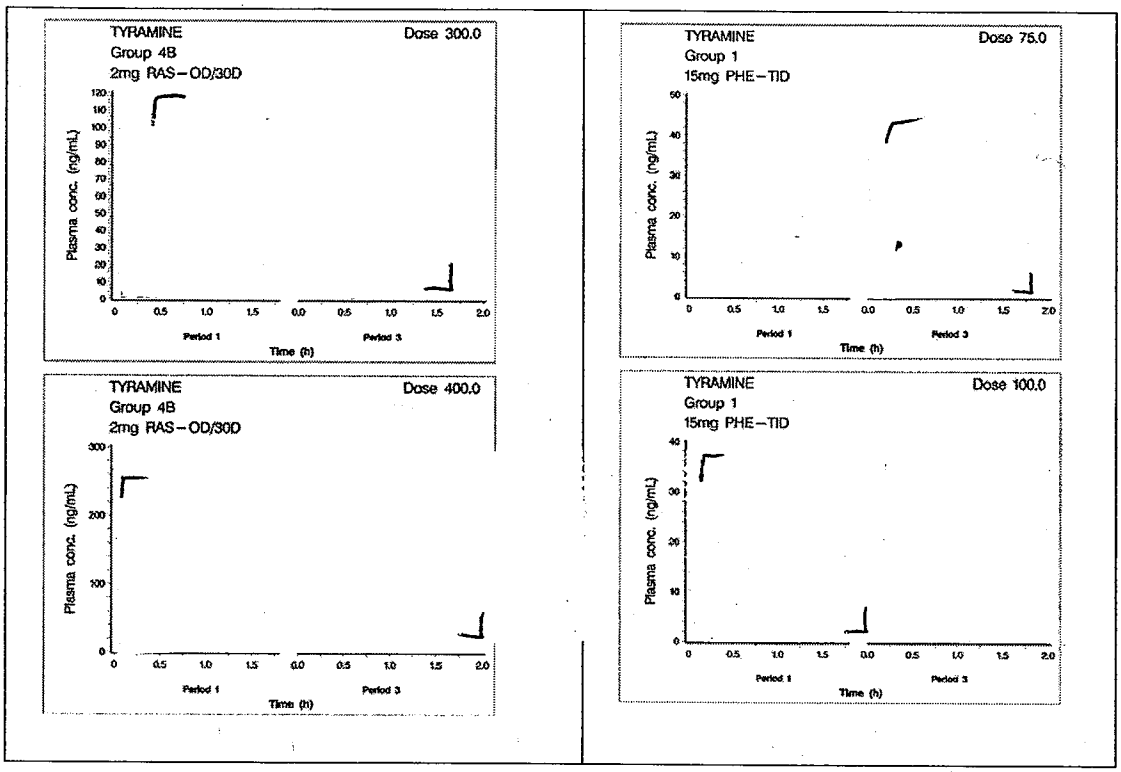

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Figure 2: Examples of Individual Tyramine Concentration-Time Profiles

Analytical method for rasagiline and 1-AI in human plasma

The analytical method involved a liquid/liquid extraction and derivatization with pentafluorobenzoylchloride followed by gas chromatography with mass spectrometric detection. The method was linear from 0.250 to 10.0 ng/mL for rasagiline and 0.500 to 10.0 ng/mL for 1-AI. The selectivity of the GC/MS method for the determination of rasagiline was demonstrated against tyramine. The performance of the assay during the sample analysis was acceptable, although 24% of the runs failed and the samples had to be reassayed.

Analytical method for DHPG in human plasma

The analytical method was validated for the determination of both DHPG and noradrenaline, however only DHPG was determined for the purpose of the study. The method involved purification on alumina followed by HPLC analysis with electrochemical detection. The analytical method was linear from 50.0 to 2000 pg/mL. As DHPG is present in human plasma, the blank plasma used for the preparation of calibration and QC samples was treated on alumina to remove endogenous DHPG. The performance of the assay during the sample analysis was acceptable.

Pharmacokinetic Results

Pharmacokinetic Results for Tyramine

Due to problems with the analytical method for analysis of tyramine in human plasma and the large number of missing samples for different time points/subjects, the PK results for tyramine were found to be interpretable.

Pharmacokinetic Results for Rasagiline and 1-AI

There was a dose-dependent increase in rasagiline and 1-AI plasma concentrations following multiple dose administration of rasagiline. In addition, mean rasagiline plasma concentration-time profiles were similar after treatment with 2 mg rasagiline for 13 days and 29 days. Rasagiline maximum mean plasma concentrations were reached about 30 minutes post-dose.

During treatment with 1 mg rasagiline (Group 3), rasagiline plasma concentrations were below LLQ during the terminal elimination phase. In addition, during treatment with 2 mg rasagiline (Groups 4a and 4b), blood samples for measurement of rasagiline plasma concentrations were collected only up to 4 hours post-dose (since these 2 cohorts were conducted prior to the Amendment), and therefore the terminal elimination phase could not be determined accurately.

Table 1: Summary Statistics of PK Parameters of Rasagiline and 1-AI

Treatment group	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)
Rasagiline					
Group 3 (N=16) (1 mg RAS-OD)	5.8 (4.0–12.7)	0.39 (0.30–0.82)	1.42 (0.62-5.36)	6.39 (3.52-16.3)	7.07 (4.04-18.0)
Group 4a (N=14)# (2 mg RAS-OD)	11.3 (2.1-21.3)	0.45 (0.32-3.07)	1.19[a] (0.91-1.19)	13.7 (4.88-21.7)	16.5[a] (10.7-23.9)
Group 4b (N=14)# (2 mg RAS-OD/30D)	15.1 (7.6-24.2)	0.38 (0.25-0.57)	1.23 (0.97-1.63)	16.2 (10.1-21.0)	17.9 (12.0-23.6)
Group 5 (N=17) (4 mg RAS-OD)	27.4 (12.5-51.6)	0.55 (0.32-0.83)	4.74 (2.30-7.41)	44.5 (28.1-76.1)	46.0 (29.1-76.1)
Group 6 (N=15) (6 mg RAS-OD)	39.0 (15.1-70.5)	0.33 (0.25-0.63)	6.78 (2.51-11.1)	64.2 (20.3-96.4)	65.6 (21.2-96.5)
1-AI					
Group 3 (N=16) (1 mg RAS-OD)	2.4 (1.7-2.9)	1.35 (0.82-3.08)	13.8 (9.25-20.4)	31.5 (15.9-48.7)	32.3 (19.1-48.8)
Group 4a (N=14)# (2 mg RAS-OD)	4.5 (2.9-8.2)	1.07 (0.82-4.07)	11.0[b] (7.12-24.3)	14.5 (9.24-25.7)	54.6[b] (34.1-90.6)
Group 4b (N=14)# (2 mg RAS-OD/30D)	5.5 (3.4-8.5)	1.08 (0.55-3.08)	13.2[c] (4.67-44.1)	18.2 (12.3-24.3)	70.8[b] (38.9-96.0)
Group 5 (N=17) (4 mg RAS-OD)	10.2 (7.4-12.7)	2.07 (0.62-3.07)	14.2 (9.63-19.2)	152 (99.5-194)	152 (99.7-194)
Group 6 (N=15) (6 mg RAS-OD)	13.1 (4.8-18.7)	1.57 (0.50-8.07)	15.8 (11.9-24.9)	190 (59.9-275)	194 (60.1-275)

For C_{max}, $t_{1/2}$, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}24}$ the geometric mean (range) is presented; for t_{max} the median (range) is presented.

#: for Groups 4a and 4b profiles were sampled only for 4 hours post-dose.

[a]: N=13; [b]: N=8; [c]: N=12

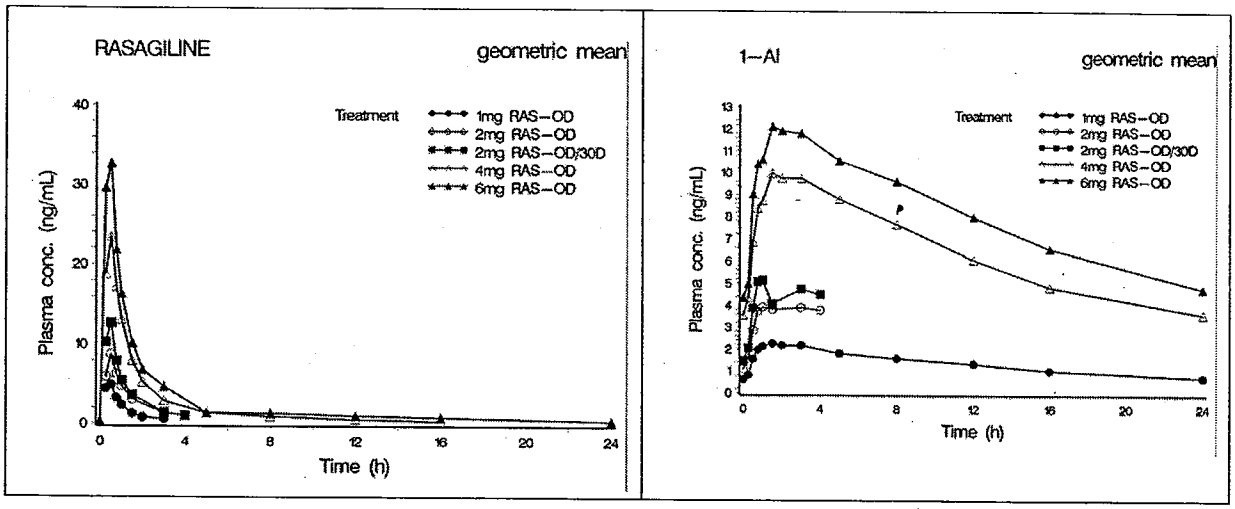

Figure 3: Mean plasma concentration-time profiles of rasagiline and 1-AI following multiple dose administration rasagiline for 13 days (29 days, group 4b)

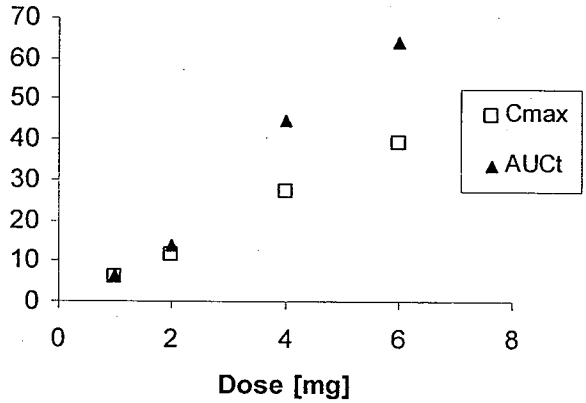

Figure 4: Rasagiline Exposure vs. Dose

Pharmacodynamic Results

DHPG (dihydroxyphenylglycol) is a metabolite of noradrenaline produced by the action of the enzyme MAO-A. DHPG plasma concentrations were used to assess the potential of rasagiline to inhibit MAO-A (mean DHPG plasma concentrations are expected to decrease after administration of a drug which inhibits MAO-A). Blood samples for the determination of DHPG concentrations in plasma were collected at baseline (Day 1) and after multiple dose administration of rasagiline, phenelzine, selegiline or placebo (Day 24 or Day 40, Group 4b).

For the positive control phenelzine and the comparator selegiline, a decrease in mean DHPG plasma concentration was observed at the studied doses, indicating MAO-A inhibition. The inhibition was stronger for phenelzine than for selegiline.
Treatment with 1 mg rasagiline for 14 days was similar to placebo in terms of mean DHPG concentrations.
After treatment with 4 mg and 6 mg rasagiline for 14 days and with 2 mg rasagiline for 30 days, a decrease mean DHPG concentrations was observed, suggesting that rasagiline became less selective for MAO-B at doses above 2 mg.

Table 2: Summary Statistics of DHPG Plasma Concentrations

Treatment	DHPG plasma concentration Day 1 (pg/mL)		DHPG plasma concentration Day 24 or Day 40 (pg/mL)				% Change	
	Baseline*		0.5 h post-dose#		2.5 h post-dose#		Baseline / 0.5 h	
Placebo (N=45)	1024	(230)	1222	(378)	1293	(317)	19.2	(21.5)
15 mg phenelzine TID (N=16)	844	(257)	633	(194)	630	(232)	-21.5	(27.3)
5 mg selegiline BID (N=15)	804	(176)[a]	762	(176)	704	(167)	-5.9	(10.5)[a]
1 mg RAS-OD (N=16)	989	(356)	1147	(208)	1155	(231)	22.1	(25.9)
2 mg RAS-OD (N=14)	1036	(310)	1024	(254)	1064	(329)	0.7	(11.4)
2 mg RAS-OD/30D (N=14)	1045	(232)	916	(178)	1022	(238)	-10.6	(13.8)
4 mg RAS-OD (N=17)	942	(229)	745	(176)	765	(206)	-19.3	(17.7)
6 mg RAS-OD (N=10)	996	(293)	773	(174)	774	(211)	-18.2	(21.1)

The arithmetic mean (SD) is presented.

* prior to tyramine dosing

\# time relative to MAOI dosing; inhibition is at steady state at end of Period 2. The % change presented is calculated based on the 0.5 h post MAOI dose measurement versus the baseline measurement.

[a] N=14

2.1.5. TVP-1012-120 Summary of PK and PD Results

- After once daily multiple dose administration of rasagiline, a dose-dependent increase in mean C_{max} and more than proportional increase in AUC plasma rasagiline values was observed in the dose range of 1 mg to 6 mg rasagiline.
- Similar exposure to rasagiline and 1-AI was observed after 14 or 30 days of daily rasagiline 2 mg.
- Maximum plasma concentrations were reached between 0.33 h and 0.55 h post-dose for rasagiline and between 1.07 h and 2.07 h for 1-AI.
- The mean half-life was between 1.19 h to 6.78 h for rasagiline and between 11.1 h to 15.8 h for 1-AI after multiple dosing with 1-6 mg rasagiline.
- The mean DHPG plasma concentrations before and after multiple dosing with 1 mg rasagiline for 14 days support the conclusion from the primary endpoint that rasagiline is selective for MAO-B at this dose level. Rasagiline became less selective for MAO-B at doses above 2 mg.

2.2 TVP-1012/TYR-400

2.1.1 Title

An Open Label, Randomized, Single Dose, Three-way Crossover Pilot Study, to Assess the Effect of Food on the Bioavailability of Tyramine Capsule and to Evaluate the Bioavailability of Tyramine, Derived from a Tyramine-Rich Meal.

2.2.2 Study Rationale

The purpose of this study was to characterize the pharmacokinetic profile of oral tyramine derived from food or from capsule (given at fasted condition or with food).
Objectives:

- To assess the effect of food on the pharmacokinetic profile of tyramine, administered as a capsule;
- To evaluate the bioavailability of tyramine, derived from a tyramine-rich meal;
- To assess the safety of tyramine, including pressor response, following different modes of administration.

2.2.3. Study Design

This was an open-label, randomized, single dose, three-period, food-effect crossover pilot study in healthy male and female subjects (N=18).
Each of the subjects was randomly assigned to one of the three study sequences.
Subjects were randomized to receive each of the following treatments:
• Administration 1 (A): 4 x 50 mg Tyramine HCl Capsule (total of 200 mg equal to 158 mg free tyramine); under fasting condition;
• Administration 2 (B): 4 x 50 mg Tyramine HCl Capsule (total of 200 mg equal to 158 mg free tyramine); with apple sauce followed 10 minutes later by a light meal;
• Administration 3 (C): Tyramine rich meal with English Stilton Cheese containing 158 mg free tyramine.

Each administration was given after an overnight fast of at least 10 hours. There was a washout period of at least 48 hours between each administration.
For each administration, 20 serial blood samples were collected per subject up to 6 hours [5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120 minutes and 2.5, 3, 3.5, 4, 5 and 6 hours postdose] following tyramine administration, for measurement of tyramine plasma levels.

2.2.4. Results

Sample analysis

Tyramine levels were measured using a validated reversed phase HPLC method with fluorescence detection. The limit of quantification (LOQ) was 0.5 ng/ml. The analytical procedure in human plasma was shown to be linear from 0.500 to 50.0 ng/ml. The performance of the method during the sample analysis was found to be acceptable.

Within each batch of study samples, at least four QC samples out of six were within ±15% (20% at the LLOQ) of their respective nominal values.

Pharmacokinetic Results

The mean (SD) plasma concentration-time curves of tyramine for the three study treatments are shown in Figure 5. Descriptive statistics and statistical analyses for tyramine pharmacokinetic parameters are presented in Table 3.

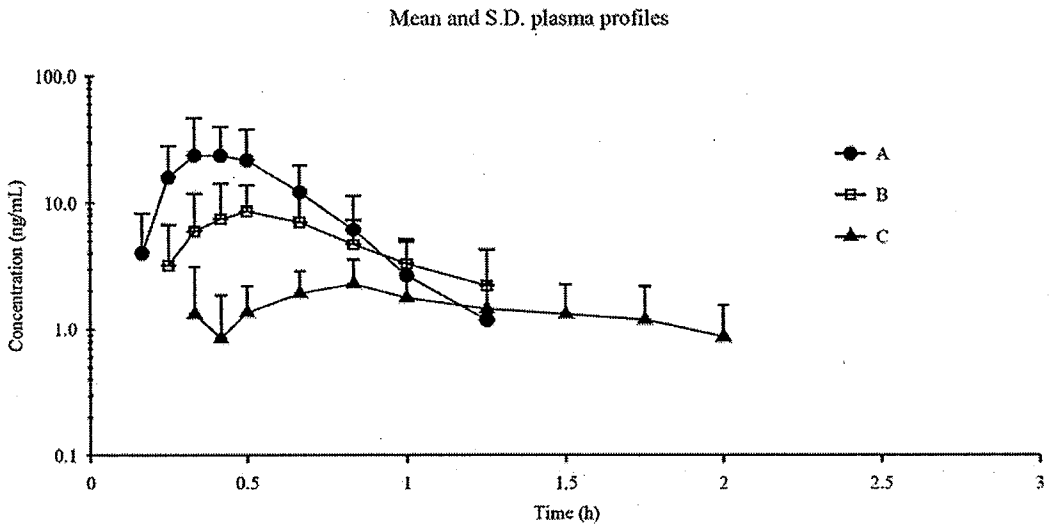

Figure 5: Mean and S.D. plasma concentration versus time profiles of Tyramine (log-linear scale)

Table 3: Dose-Normalized Tyramine Pharmacokinetic Parameters

TYRAMINE (N=18)		C_{max}/dose (ng/mL)	AUC_{0-t}/dose (h*ng/mL)	$AUC_{0-\infty}$/dose* (h*ng/mL)
Treatment A	Mean	0.223	0.079	0.091
	SD	0.150	0.037	0.046
	CV (%)	67	47	51
Treatment B	Mean	0.067	0.038	0.054
	SD	0.043	0.025	0.027
	CV (%)	64	65	49
Treatment C	Mean	0.027	0.024	0.053
	SD	0.031	0.013	0.021
	CV (%)	115	53	39
90% confidence Interval				
Treatment B *vs.* Treatment A		0.23-0.40	0.38-0.55	0.46-0.91
Treatment C *vs.* Treatment A		0.08-0.14	0.25-0.37	0.46-0.91
Treatment C *vs.* Treatment B		0.27-0.47	0.55-0.80	0.71-1.40
Point estimate				
Treatment B *vs.* Treatment A		0.30	0.46	0.65
Treatment C *vs.* Treatment A		0.11	0.30	0.65
Treatment C *vs.* Treatment B		0.36	0.66	1.00

#Median (min-max) value

*N=10 (only subjects with $AUC_{0-\infty}$ for the three treatments were kept in the statistical analysis)

- The mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of tyramine were significantly decreased by 70%, 54% and 35%, respectively when a capsule of tyramine was administered with apple sauce followed with a light meal compared to fasting conditions. Moreover, t_{max} was significantly delayed from 25 min to 50 min.
- After administration of the tyramine rich meal (Stilton cheese), the terminal elimination slope was not determined accurately (bad fitting, $r < 0.95$, AUC extrapolated > 20%), therefore $AUC_{0-\infty}$ and $t_{1/2}$ values should be interpreted with caution. Consequently the AUC_{0-t} appeared to be a better estimator of the overall extent of absorption of tyramine and was used instead of $AUC_{0-\infty}$ for statistical comparison. Moreover, as the amount of cheese administered to each subject was different, the dose normalised PK parameters were statistically compared.
- The mean dose normalised C_{max} and AUC_{0-t} of tyramine were 89% and 70% lower after administration of a tyramine-rich meal, compared to tyramine administered under fasting conditions. Moreover, t_{max} was significantly delayed after a tyramine-rich meal from 25 min to 50 min.
- After administration of a tyramine-rich meal, the mean dose normalized C_{max} and AUC_{0-t} of tyramine were 60% and 37% lower compared to tyramine derived from a capsule administered under fed conditions. Moreover, t_{max} was significantly delayed after dietary tyramine compared to tyramine with apple sauce followed by a meal (i.e. 50 min vs. 30 min).

2.1.5. Summary

- Food significantly decreases the bioavailability of tyramine administered as a capsule
- Tyramine derived from a tyramine-rich meal of Stilton cheese has a very low bioavailability compared to tyramine from a capsule given under either fed of fasting conditions
- All treatments were well tolerated and no clinically significant changes from screening occurred. No adverse events occurred that could have been considered a tyramine reaction.

3. Conclusions

The results from tyramine challenge study suggest increased sensitivity for rasagiline treatment at doses above 2 mg daily, therefore factors (e.g., age, gender, DDI, renal or hepatic impairment) that significantly increase rasagiline exposure should be labeled as a need to reduce the daily dose and/or follow tyramine dietary restriction. A summary of intrinsic and extrinsic factors which could potentially affect rasagiline exposure is provided below.

- Rasagiline is primarily metabolized by CYP1A2. Strong CYP1A2 inhibitors like fluvoxamine and ciprofloxacin are expected to increase rasagiline exposure. A drug interaction study demonstrated an 83% increase in AUC for rasagiline in the presence of steady-state ciprofloxacin. There was no effect of theophylline (a CYP1A2 substrate) on rasagiline when they were co-administered.
- Hepatic impairment has a significant effect on rasagiline exposure. Rasagiline exposure at steady-state was two-fold increased in subjects with mild hepatic impairment compared to healthy subjects and up to 7 fold increased in moderately hepatic impaired subjects.
- Renal impairment is not expected to have an effect on rasagiline exposure, since less than 0.5% of the dose is excreted unchanged in the urine. A study in renaly impaired patients demonstrated that rasagiline exposure was comparable for healthy subjects and subjects with moderate renal impairment following once daily repeated dosing of 1 mg rasagiline for 8 days. However, metabolite 1-aminoindan (1-AI) exposure was increased 1.5- fold in subjects with moderate renal impairment.
- A dose-proportionality study demonstrated a dose-dependent increase in mean C_{max} and more than proportional increase in mean AUC plasma rasagiline values in the 1 mg to 6 mg/day dose range following multiple-dose administration in healthy young and elderly subjects. The results from this study also showed little effect of age and concomitant administration of levodopa/carbidopa on rasagiline PK.

- Population analysis did not find any significant gender differences following 1 mg once daily dosing. Females had slightly higher AUC than males, which could be accounted by differences in body weight.
- The concomitant intake of rasagiline with food decreased the C_{max} and AUC by 60% and 20% respectively.

4. Recommendations

The clinical study reports in this submission are considered to fulfill the Phase 4 commitment from a clinical pharmacology perspective. The reviewer's labeling recommendations are shown by track changes to the sponsor proposed label. These labeling changes should be incorporated in the revised label.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AZILECT® safely and effectively. See full prescribing information for AZILECT®.

AZILECT® (rasagiline mesylate) Tablets for Oral Use
Initial U.S. Approval: 2006

b(4)

b(5)

26 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_X_ Draft Labeling (b4)

_X_ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Personal Privacy (b6)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21641	SUPPL-8	TEVA NEUROSCIENCE INC	AZILECT (RASAGILINE MESYLATE) 1MG TABLET

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/s/

HRISTINA DIMOVA
12/04/2009

YUXIN MEN
12/06/2009