4 STUDY TVP-1012/TYR-400 RESULTS

This reviewer also directs the reader's attention to the Clinical Pharmacology Review by Dr. Kristina Dimova.

2 SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceutical Industries **Name of Active Ingredients:** Tyramine	**Protocol No.: TYR-400**	**(For National Authority Use Only)**
Study 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.		
Study Site Investigator and Respective Study Site Dr Jacob Atsmon STCRC Tel-Aviv Sourasky Medical Center 6 Weizmann St. Tel-Aviv 64239, ISRAEL		
Publication Based on Study Results Not Applicable		
Study Dates First Subject Enrolled: 19 December 2004 Last Subject Completed Trial: 24 February 2005		**Clinical Phase** Phase I
Study Treatments, Dose and Mode of Administration Treatment A: 4 x 50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine); Fasting Treatment B: 4 x 50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine); with apple sauce followed 10 minutes later by a light meal. Treatment C: Tyramine rich meal made of English Stilton Cheese containing 158 mg *free* tyramine		
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.		
Methodology This was an open-label, single dose, three treatment, three-period, three-sequence, food-effect crossover pilot study. A total of 18 healthy male and female subjects received three study treatments each of which was separated by a 48-hour wash-out interval: Treatments were given according to one of three sequences (A-B-C, B-C-A or C-A-B) to which subjects were equally randomized. Subjects were housed at the study center from the night prior to the dosing of each treatment until 8 hours after dosing. Throughout this period, subjects remained under constant medical and nursing observation. They had to refrain from strenuous physical activities. They were permitted to read, write, watch television and play cards. Blood samples were taken according to predetermined times from pre-dose until 6 hours following tyramine administration [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 post-dose] for measurement of tyramine plasma levels. Tyramine levels were measured using a validated reversed-phase HPLC method with fluorescence detection. The limit of quantification (LOQ) was 0.5 ng/ml. Concentration-time curves were drawn up for each volunteer for each treatment, and these allowed for the determination of the relevant PK parameters.		
Diagnosis and Main Criteria for Inclusion Healthy male and female volunteers		

Name of Sponsor/Company: Teva Pharmaceutical Industries **Name of Active Ingredients:** Tyramine	**Protocol No.: TYR-400**	**(For National Authority Use Only)**

Duration of Treatment:
3 study treatments each separated by a 48-hour wash out interval

Criteria for Evaluation

Pharmacokinetics

- Partial and total area under the concentration-time curve (AUC_{0-t}, $AUC_{0-\infty}$)
- Peak concentration (C_{max})
- Time to peak concentration (t_{max})
- Half-life ($t½$) and elimination rate constant (λz)

Safety

Recording of adverse events (AEs)

- Vital signs (blood pressure and pulse rate measurements)
- 12-lead ECG
- laboratory tests (biochemistry, hematology and urinalysis)

Statistical Methods

Individual and mean plasma concentrations of tyramine were tabulated at each time-point following each treatment. Summary statistics [mean, SD, median, maximum, minimum and the number of observations (n)] were calculated. For the calculation of these statistics, tyramine concentrations below the limit of quantitation (0.5 ng/ml) were substituted with zero. Individual plasma concentration/time curves were drawn on linear/linear and linear/log scales for each treatment.
Mean plasma concentrations versus time profiles are presented on linear/linear plot for each treatment.
Individual pharmacokinetic parameters (Cmax, tmax, $t½$, λz, and partial and total AUC) and the mean, SD, median, maximum, and minimum values are tabulated for each treatment.

SUMMARY-RESULTS

Patient Disposition

Altogether 20 subjects were screened for study eligibility. Two subjects were found to be unsuitable. The remaining 18 subjects participated in this study and completed the 3 study periods.
Treatments were administered according to 3 possible sequences: A-B-C, B-C-A or C-A-B. Subjects were equally randomized to one of the 3 sequences.
All of the 18 subjects were Caucasian - 11 male and 7 female. The overall mean age of the study population was 45 years. All subjects were within the required body mass index of 18.5 to 30 kg/m^2, with a mean value of 25.5 kg/m^2.
No subject entered the study with any clinically significant medical condition. All subjects were non-smokers.

Pharmacokinetic Results

The pharmacokinetics of tyramine administered as a capsule differed markedly between fasting and non-fasting conditions. Maximal absorption occurred later when tyramine was taken with food, and Cmax and AUC were significantly decreased compared to fasting conditions.
The pharmacokinetic parameters of tyramine were dramatically lower when administered as a tyramine rich meal with Stilton cheese (Treatment C) as compared to the tyramine capsule administered either under fed (Treatment B) or fasting conditions (Treatment A). Indeed, the mean dose normalized Cmax were about 8 and 3-times lower for tyramine rich meal with Stilton cheese compared to tyramine administered as a capsule in fasting state and in apple sauce followed by a meal, respectively. The mean normalized AUC0-t were 2 to 3

Name of Sponsor/Company: Teva Pharmaceutical Industries Name of Active Ingredients: Tyramine	Protocol No.: TYR-400	(For National Authority Use Only)

times lower for dietary tyramine compared to the capsule. Moreover, the absorption of dietary tyramine was significantly delayed compared to tyramine administered as a capsule in fasting conditions and with apple sauce followed by a meal.

Safety Results

The most commonly reported AE was headache for which there were 3 reports during treatment A, and 6 reports during each of treatments B and C from a total of 18 subjects. Of the 15 reports of headache only one was moderate while all others were mild in nature although 9 cases were treated with acetaminophen.

The only other AE that was reported by more than one subject was dizziness. It was reported by one subject during treatment A and another subject during treatment B. In both cases it was transient and required no corrective treatment.
No SAEs occurred during the study.

OVERALL CONCLUSIONS AND DISCUSSION

- Food significantly decreases the bioavailabilty 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 or 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.

Additional Study Report Information/Details

Treatments Administered

All subjects received the following 3 treatments:

Treatment A: 200 mg tyramine HCl capsules (four 50 mg capsules) swallowed whole with 150 ml mineral water at room temperature.

Treatment B: The four 50mg tyramine HCl capsules opened and all their content mixed with 113 gram of applesauce. Tyramine was given 10 minutes before a standardized morning meal consisting of a 2 medium sized egg omelet fried in one teaspoon of margarine along with a cup of coffee (200 ml with 2 tablespoon of skimmed milk and 1 teaspoon of sugar) (approximately 200 kcal, 10 gram protein and 15 gram fat, based on USDA National Nutrient Database for Standard Reference). The meal should have been consumed within 15 minutes.

Treatment C: Tyramine was given as a tyramine-rich meal. The subject ate English Stilton Cheese containing 158 mg tyramine, served with slices of one toasted pita bread, one cucumber and one tomato, within **30** minutes. Subjects were permitted to drink 300 ml water. The leftovers of cheese that was not eaten within 30 minutes was weighed and recorded.

Reviewer Comments

- This reviewer has significant interest in the bioavailability of tyramine contained in food (e.g., Treatment C) because that is how patients treated with an MAO inhibitor might be exposed to a significant amount of bioavailable tyramine that could potentially cause a hypertensive crisis/"cheese" reaction if the MAO inhibitor produced a sufficient increase in tyramine sensitivity. Consequently, much of my interest in this study will focus on Treatment C.

- It is not known nor whether the concomitant ingestion of the additional food (i.e., bread, cucumber, and tomato) might have altered the tyramine bioavailability of the Stilton cheese as did food administered along with tyramine hydrochloride added to food in Treatment B.

- This additional food (i.e., bread, cucumber, and tomato) could be consumed at various times within 30 minutes of ingesting the Stilton cheese by various individuals. This lack of standard concomitant ingestion time of this additional food could possibly contribute to variability of tyramine bioavailability in the Stilton cheese.

In treatment C, estimated cheese and tyramine consumption is summarized and shown below here in Table 1..

Table 1: Treatment C: Stilton Cheese consumed

Subject #	Subject Initials	Cheese Period	Cheese Administered (g)	Cheese consumed (g)	Consumed Free Tyramine (mg)*	Tyramine Dose (%)
1		III	185	185	158.0	100.0
2		II	185	185	158.0	100.0
03a		I	185	134.1	114.5	72.5
04a		III	185	185	158.0	100.0
5		I	185	88	75.2	47.6
6		II	185	185	158.0	100.0
7		III	160	159.7	157.7	99.8
8		I	160	99.2	98.0	62.0
9		II	160	53.7	53.0	33.5
10		II	160	122.7	121.2	76.7
11		I	160	117.6	116.1	73.5
12		III	160	159.7	157.7	99.8
13		III	202.5	202.2	157.8	99.9
14		I	202.5	201.9	157.5	99.7
15		II	202.5	200.2	156.2	98.9
16		III	202.5	202	157.6	99.7
17		II	202.5	202.1	157.7	99.8
18		I	202.5	201.2	157.0	99.4

b(6)

*200mg tyramine capsule contains 158mg free tyramine. Each group of 6 subjects was administered a cheese amount containing 158mg free tyramine, as follows:
#Subjects 1-6, Cheese block C-D test # 51/10905: The mean of 853.5mg free tyramine/kg cheese (%RSD =8), required 185.2g cheese per subject
#Subjects 7-12, Cheese block 2, test # 51/12452: The mean of 987mg free tyramine/kg cheese (%RSD =8), required 160.0g cheese per subject
#Subjects 13-18, Cheese block 1 test # 51/12452: The mean of 780mg free tyramine/kg cheese (%RSD =7), required 202.5g cheese per subject

Reviewer Comments

- Table 1 above here shows that most individuals were considered to have ingested essentially the full, or maximally administered/planned tyramine (free) challenge. Some individuals Some subjects (# 3a,5,8,9,10,), including two subjects who experienced at least a single threshold (≥ 30 mm hg) SBP increase after Treatment C, were believed to have ingested notably less than the planned, maximal tyramine challenge (158 mg free tyramine). .

PHARMACOKINETIC (PK) EVALUATION

The mean (SD) plasma concentration-time curves of tyramine for the three study treatments are shown in Figure 1 (log-linear scale) and descriptive statistics and statistical analyses for pharmacokinetic parameters are presented in Table 1 and Table 2. Figure 6.3.3 shows the PK plasma tyramine profiles for all individuals treated with the tyramine-rich Stilton cheese (Treatment C) on a linear-linear scale (upper panel) and on a log-linear scale (lower panel).

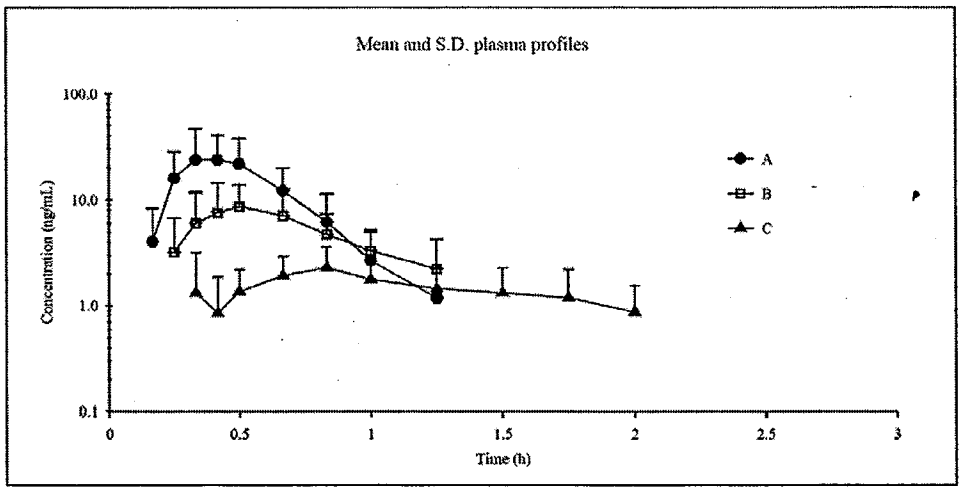
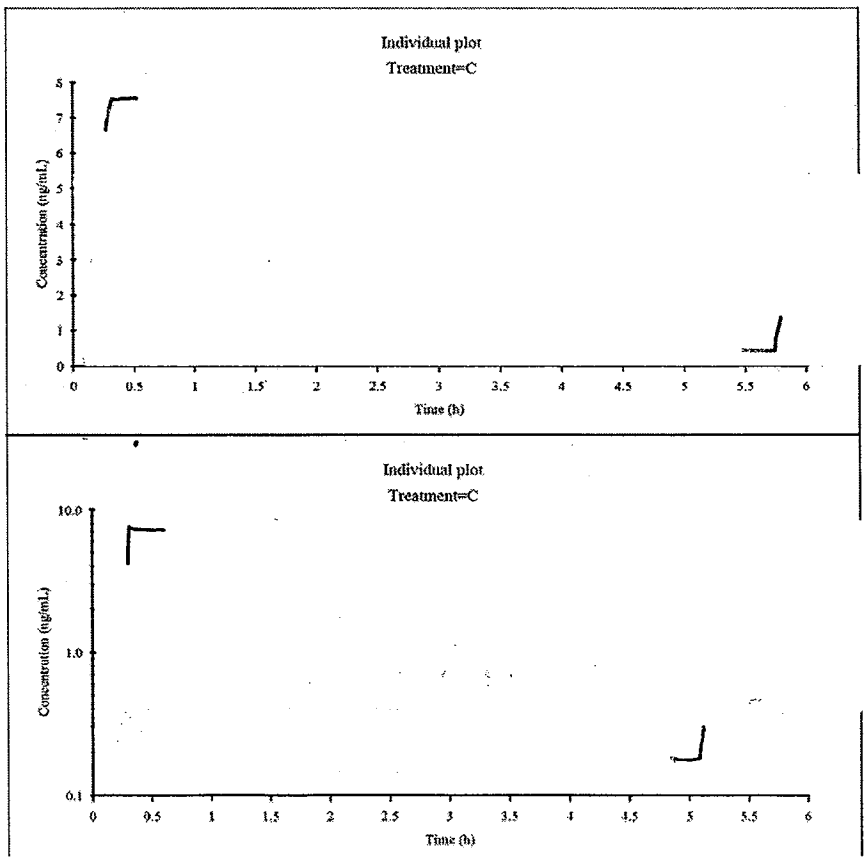


Figure 1. Mean and S.D. plasma concentration versus time profiles of Tyramine (log-linear scale lower)

6.3.3 Tyramine - Treatment C: Tyramine rich meal with Stilton cheese (linear scale: upper – log-linear scale: lower)



b(4)

Reviewer Comments

- It is visually apparent in Figure 1 that administering oral tyramine hydrochloride with applesauce followed by a meal (Treatment B) is associated with a significant decrease in mean Cmax and also mean AUC for tyramine compared to the same amount of tyramine administered under fasting conditions (Treatment A). Decreased tyramine bioavailability during the sponsor's previously conducted tyramine challenge studies in which a relatively low dose of tyramine was administered with applesauce or ice cream followed soon after with a meal was a theoretical concern during our original review of rasagiline (NDA 21641). More specifically, **I had raised the question whether the lack of showing rasagiline-induced increased tyramine sensitivity in these studies was possibly a false negative response related to possible decreased tyramine bioavailability because of the apple sauce or ice cream and subsequent meal that soon after followed. Based upon these tyramine PK results in this study (TYR 400), it now appears that the lack of increased tyramine sensitivity responses certainly could have been false negatives because of decreased tyramine bioavailability related to the tyramine in applesauce and meal ingested soon after the tyramine administration.**

- It is also visually apparent in Figure 1 that administering oral tyramine in an aged cheese (e.g., Stilton) with some additional food (bread, cucumber, tomato, Treatment C) is associated with a significant decrease in mean Cmax and also mean AUC for tyramine compared to the same amount of tyramine administered under fasting conditions (Treatment A) and with applesauce soon after followed by a meal (Treatment B).

- Overall, the mean tyramine plasma profile for Treatment C is markedly flattened with Cmax occurring just before 1 hour compared to the other two treatments. However, Figure 6.3.3 shows that some subjects treated with Treatment C exhibited clear cut, sharp spikes in Cmax indicating that there can be considerable variability in the shape of the plasma tyramine profile after ingestion of a tyramine-rich food such as Stilton cheese. Except that the Tmax for most subjects administered Treatment C is delayed, the shape of plasma profile of some of these subjects appears to be quite similar to the mean PK profile (and individual subject PK profiles) of subjects administered tyramine hydrochloride under fasting conditions (Treatment A).

Table 1. Tyramine Pharmacokinetic Parameters

TYRAMINE (N=18)		t_{max}# (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	$AUC_{0-\infty}$* (h*ng/mL)
Treatment A	Mean	0.42	35.3	12.49	14.42
	SD		23.7	5.89	7.34
	CV (%)	0.25-0.67	67	47	51
Treatment B	Mean	0.50	10.7	6.03	8.58
	SD		6.87	3.94	4.23
	CV (%)	0.25-0.83	64	65	49
Treatment C	Mean	0.83	2.96	3.20	7.12
	SD		1.57	1.88	3.79
	CV (%)	0.25-1.75	53	59	53
90% confidence Interval					
Treatment B *vs.* Treatment A		$p < 0.05$ (1)	0.23-0.39	0.37-0.57	0.44-0.96
		$p < 0.001$ (1)	0.07-0.12	0.20-0.31	0.36-0.79
Treatment C *vs.* Treatment A		$p < 0.05$ (1)	0.23-0.38	0.45-0.69	0.56-1.21
Treatment C *vs.* Treatment B					
Point estimate					
Treatment B *vs.* Treatment A			0.30	0.46	0.65
			0.09	0.25	0.54
Treatment C *vs.* Treatment A			0.3	0.55	0.82
Treatment C vs. Treatment B					

#Median (min-max) value
*N=10 (only subjects with $AUC_{0-\infty}$ for the three treatments were kept in the statistical analysis)
(1): Wilcoxon Signed Rank Test

Table 2. 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)

Bioavailability of tyramine derived from a capsule administered with apple sauce followed by a meal versus tyramine derived from a capsule administered under fasting conditions (Treatment B vs A)

When a capsule of tyramine was administered with apple sauce followed 10 minutes later with a light meal, the mean Cmax, AUC0-t and AUC0-∞of tyramine were significantly decreased by 70%, 54% and 35% compared to fasting conditions, respectively. These results were supported by point estimates (0.30 for Cmax and 0.46 for AUC0-t and 0.65 for AUC0-∞) and by the 90% confidence intervals which were outside the bioequivalence range 0.80-1.25 (see above Table 1). Moreover, tmax was significantly delayed.

Bioavailability of tyramine derived from a tyramine-rich meal of Stilton Cheese versus tyramine derived from a capsule administered under fasting conditions (Treatment C vs A)

After administration of the tyramine rich meal (Stilton cheese), as the terminal elimination slope was not determined accurately (bad fitting, $r < 0.95$, AUC extrapolated > 20%), AUC0-∞and t1/2 values should be considered with caution. Consequently the AUC0-t appeared to be a better

estimator of the overall extent of absorption of tyramine than AUC0-∞and was used as the target parameter instead of AUC0-∞for statistical comparison. Moreover, as the amount of cheese administered to each subject was different, an additional analysis was performed in which dose normalized parameters were statistically compared (see Table above 2). After administration of a tyramine-rich meal, the mean dose normalized Cmax and AUC0-t of tyramine were 89% and 70% lower compared to tyramine administered under fasting conditions. This was confirmed by the point estimates (0.11 and 0.30 for Cmax and AUC0-t) and the 90% confidence intervals which were completely outside the bioequivalence range of 0.80-1.25 (see above Table 2). Moreover, tmax was significantly delayed after a tyramine-rich meal from 25 min to 50 min.

Bioavailability of tyramine derived from a tyramine-rich meal of Stilton Cheese versus tyramine derived from a capsule administered under fed conditions (Treatment C vs B)

After administration of a tyramine-rich meal, the mean dose normalized Cmax and AUC0-t of tyramine were 60% and 37% lower compared to tyramine derived from a capsule administered under fed conditions. This was confirmed by the point estimates (0.36 and 0.66 for Cmax and AUC0-t) and the 90% confidence intervals which were completely outside the bioequivalence range of 0.80-1.25 (see above Table 2). Moreover, tmax was significantly delayed after dietary tyramine compared to tyramine with apple sauce followed by a meal (i.e. 50 min *vs.* 30 min).

Table 7.3.1 shows individual subject PK parameters for Cmax and AUC for Treatment A.

7.3.1. (continued) Individual pharmacokinetic parameters of tyramine - Treatment A: 4 x 50 mg Tyramine HCL capsule in fasting conditions

Subject	Gender	C_{max}/dose* (ng/mL/mg)	AUC_{0-t}/dose* (h*ng/mL/mg)	$AUC_{0-\infty}$/dose* (h*ng/mL/mg)
1	Male	0.110	0.082	0.084
2	Male	0.160	0.036	0.037
3	Female	0.124	0.063	0.064
4	Male	0.143	0.055	0.058
5	Male	0.152	0.048	0.049
6	Male	0.120	0.050	NC
7	Male	0.052	0.021	0.022
8	Female	0.450	0.105	0.107
9	Female	0.226	0.083	0.083
10	Female	0.339	0.155	0.159
11	Female	0.458	0.137	0.139
12	Male	0.169	0.083	0.084
13	Male	0.113	0.031	0.032
14	Male	0.627	0.118	0.128
15	Female	0.170	0.097	0.108
16	Female	0.200	0.072	NC
17	Male	0.240	0.118	0.120
18	Male	0.169	0.070	0.071

*dose = 158 mg free tyramine

Reviewer Comments

- Individual C_{max}/dose and AUC_{0-t}/dose show significant variability (from lowest to highest value ~ 12 and 6 fold respectively) relative to mean C_{max}/dose (0.223) and mean AUC_{0-t}/dose (0.079) for Treatment A.

Table 7.3.2 shows individual subject PK parameters for Cmax and AUC for Treatment B.

7.3.2. (continued) Individual pharmacokinetic parameters of tyramine - Treatment B: 4 x 50 mg Tyramine HCL capsule with apple sauce followed by a light meal

Subject	Gender	C_{max}/dose* (ng/mL/mg)	AUC_{0-t}/dose* (h*ng/mL/mg)	$AUC_{0-\infty}$/dose* (h*ng/mL/mg)	Frel (B/C) (AUC_{0-t}/dose)	Frel (B/C) ($AUC_{0-\infty}$/dose)
1	Male	0.091	0.048	0.050	1.49	NC
2	Male	0.080	0.024	0.025	2.05	NC
3	Female	0.076	0.052	0.055	1.96	1.22
4	Male	0.053	0.027	0.036	1.21	1.33
5	Male	0.040	0.024	0.028	1.39	NC
6	Male	0.034	0.017	0.020	1.38	0.76
7	Male	0.027	0.022	0.033	1.64	0.73
8	Female	0.063	0.029	NC	1.81	NC
9	Female	0.120	0.055	0.056	1.40	0.97
10	Female	0.178	0.091	0.096	2.83	2.43
11	Female	0.078	0.066	0.069	1.66	1.31
12	Male	0.023	0.011	0.013	1.05	NC
13	Male	0.035	0.027	0.031	1.33	0.30
14	Male	0.050	0.028	0.031	0.80	0.61
15	Female	0.054	0.034	0.036	1.58	0.92
16	Female	0.032	0.018	0.019	1.79	1.02
17	Male	0.147	0.096	0.102	1.72	1.46
18	Male	0.032	0.017	0.020	1.12	NC

*dose = 158 mg free tyramine

Reviewer Comments

- Individual C_{max}/dose and AUC_{0-t}/dose show significant variability (from lowest to highest value ~ 8 and 9 fold respectively) relative to mean C_{max}/dose (0.067) and mean AUC_{0-t}/dose (0.038) for Treatment B.

Table 7.3.3 shows individual subject PK parameters for Cmax and AUC for Treatment C.

7.3.3 (continued) Individual pharmacokinetic parameters of tyramine - Treatment C: Tyramine rich meal with Stilton cheese

Subject	Gender	C_{max}/dose* (ng/mL/mg)	AUC_{0-t}/dose* (h*ng/mL/mg)	$AUC_{0-\infty}$/dose* (h*ng/mL/mg)	Frel (C/A) (AUC_{0-t}/dose)	Frel (C/A) ($AUC_{0-\infty}$/dose)
1	Male	0.023	0.032	NC	0.39	NC
2	Male	0.010	0.012	NC	0.33	NC
3	Female	0.030	0.026	0.045	0.42	0.70
4	Male	0.017	0.023	0.027	0.41	0.46
5	Male	0.042	0.017	NC	0.37	NC
6	Male	0.012	0.012	0.027	0.25	NC
7	Male	0.012	0.013	0.045	0.64	2.03
8	Female	0.019	0.016	0.045	0.15	0.42
9	Female	0.144	0.040	0.058	0.48	0.69
10	Female	0.019	0.032	0.039	0.21	0.25
11	Female	0.044	0.040	0.053	0.29	0.38
12	Male	0.018	0.011	NC	0.13	NC
13	Male	0.019	0.020	0.101	0.65	3.12
14	Male	0.017	0.035	0.050	0.29	0.39
15	Female	0.013	0.022	0.039	0.23	0.36
16	Female	0.009	0.010	0.019	0.14	NC
17	Male	0.030	0.056	0.070	0.47	0.58
18	Male	0.009	0.015	NC	0.22	NC

*dose = free tyramine

- Individual C_{max}/dose and AUC_{0-t}/dose show significant variability (from lowest to highest value ~ 15 and 6 fold respectively) relative to mean C_{max}/dose (0.0.027) and mean AUC_{0-t}/dose (0.024) for Treatment C.

Vital Signs:
Supine blood pressure and heart rate measurements were taken at the following times: Pre-dose, 5, 10, 15, 20, 25, 30, 40, 50, 60, 80, 100, 120, 140, 160 minutes, 3, 3.5, 4, 5, 6 and 8 hours after dosing. Subjects who experienced significant blood pressure elevations (≥ 30 mmHg increase from the pre-tyramine baseline value), heart rate reduction (bradycardia with heart rate ≤ 40 bpm lasting for 10 minutes or more), or adverse events that could have suggested a tyramine reaction in the opinion of the investigator (e.g. headache) at any time during the active monitoring period, would have had SBP and heart rate measured every 5 minutes until a decrease of ≥ 15 mmHg from the significant high blood pressure measurement was noted over 3 consecutive readings, or until heart rate returned to baseline or the AE resolved.

There was no noteworthy nor clear effect of any tyramine treatment on mean systolic or diastolic blood pressure.

The following Table 9 shows the incidence of subjects who had at least a single, threshold, SBP increase (relative to single, pre-treatment measurement) of 30 mm Hg or more on at least one occasion. If a subject had more than one threshold increase, the subject is only counted once in the incidence data for all subjects according to each treatment (A, B, or C).

Post-Text Table 9. Distribution of Subjects with an increase from pre-dose in SBP of at least 30 mmHg

TYR400	A		B		C	
	N	%	N	%	N	%
10 min post-dose	.	.	1	5.6	.	.
15 min post-dose	.	.	2	11.1	.	.
20 min post-dose	.	.	1	5.6	.	.
25 min post-dose	.	.	.	.	1	5.6
30 min post-dose	.	.	.	.	2	11.1
160 min post-dose	.	.	.	.	1	5.6
3.5 hr post-dose	.	.	.	.	1	5.6
4 hr post-dose	1	5.6	.	.	.	.
5 hr post-dose	.	.	.	.	1	5.6
8 hr post-dose	.	.	.	.	1	5.6
All	1	5.6	3	16.7	4	22.2

Reviewer Comments

- The tyramine threshold response (SBP increase of at least 30 mm Hg on at least one occasion) for 200 mg tyramine hydrochloride (158 mg free tyramine) was met for only 1 subject (5.6 %) who received tyramine HCl under fasting conditions. This percentage at this dose is similar to what was observed for all subjects in Study 120 who underwent open-label, baseline/pre-treatment testing. However, the percentage was higher for subjects receiving 158 mg free tyramine with food (Treatment B, 17 %) or in Stilton cheese with some other food (Treatment C, 22 %). Considering that the Cmax and AUC was substantially decreased for each of these treatments compared to fasting tyramine

(Treatment A), these results seem somewhat surprising and counter-intuitive as to what might be expected.

A critical issue is that it is not clear if the tyramine threshold pressor response is real and because this study was not conducted requiring the more rigorous study conditions used in Study 120 for assessing tyramine threshold pressor responses. This study (# 400) used a single, baseline/pre-treatment BP measurement (for comparison with post-tyramine measurements) instead of the average of 3 baseline/pre-treatment measurements and did not require 3 consecutive sustained SBP increases of at least 30 or more mm Hg to be considered a "true," threshold, pressor response.

If these threshold responses with tyramine administered in food (e.g., Stilton cheese) are real, one might also theoretically expect that if tyramine sensitivity were increased by rasagiline treatment (even 1 mg daily) that the percentage of tyramine threshold responses might be even further increased in percentage, (e.g., > 22 %).

SPONSOR DISCUSSION AND CONCLUSIONS

The objective of this study was to characterize the comparative pharmacokinetic profile of oral tyramine derived from food or from capsule (given at fasted condition or with food).
The pharmacokinetics of tyramine administered as a capsule differed markedly between fasting and non-fasting conditions. Maximal absorption occurred later when tyramine was taken with food, and Cmax and AUC were significantly decreased compared to fasting conditions.

The pharmacokinetic parameters of tyramine were dramatically lower when administered as a tyramine rich meal with Stilton cheese (Treatment C) as compared to the tyramine capsule administered either under fed (Treatment B) or fasting conditions (Treatment A). Indeed, the mean dose normalized Cmax were about 8 and 3-times lower for tyramine rich meal with Stilton cheese compared to tyramine administered as a capsule in fasting state and in apple sauce followed by a meal, respectively. The mean normalized AUC0-t were 2 to 3 times lower for dietary tyramine compared to the capsule. Moreover, the absorption of dietary tyramine was significantly delayed compared to tyramine administered as a capsule in fasting conditions and with apple sauce followed by a meal.

It can be concluded from this study that :
. 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.

The following subject data listing shows details about subjects who experienced at least one threshold SBP of ≥ 30 mm Hg compared to a single BP measurement at pre-treatment.

Data Listing of Subjects with an Increase from Pre-Dose in SBP of at least 30 mmHg

Subject No	Volunteer Initials	Period	Treatment	Time in Minute Post Dose	SBP Post Dose	SBP Pre Dose	Change From Pre Dose
8		THREE	B	10 min post-dose			
		TWO	A	4 hr post-dose			
12		TWO	B	15 min post-dose			
			B	20 min post-dose			
18		THREE	B	15 min post-dose			
10		TWO	C	25 min post-dose			
11		ONE	C	30 min post-dose			
13		THREE	C	30 min post-dose			
4.1		THREE	C	160 min post-dose			
			C	3.5 hr post-dose			
			C	5 hr post-dose			
			C	8 hr post-dose			

b(6)

b(4)

Reviewer Comments

- **My subsequent review here will focus on trying to make some assessment about whether the tyramine threshold, pressor responses observed in the 4 subjects (# 10, 11, 13, 4/ or 4.1) who experienced such a response with Treatment C (Stilton cheese) seemed to be "real," bonfire responses based upon the review of the SBP measurements and also the plasma tyramine levels.**

Subject No.	Period	Treatment	Dosing Date	Time Relevant to Dose (Min/hours)	Theoretical Time	Supine BP Actual Time	SBP mmHg	DBP mmHg	PULSE bpm	Blood Sample Actual Time	ECG	Meals	Comments	Released from the CRC
10.0	1	B	14FEB2005	160min	10:49	10:49				.				
				3hrs	11:09	11:09				11:09				
				3.5hrs	11:39	11:39				11:39				
				4hrs	12:09	12:09				12:09	Yes			
				5hrs	13:09	13:09				13:09				
				5.5hrs	13:39	.				.		Yes		
				6hrs	14:09	14:10				10:09	Yes			
				8hrs	16:09	16:15				.	Yes			Yes
	2	C	16FEB2005	Pre Dose		7:16				7:30	Yes			
				0(Dosing)	08:09	.				.				
				5min	08:14	8:14				8:14				
				10min	08:19	8:19				8:19				
				15min	08:24	8:24				8:24				
				20min	08:29	8:29				8:29	Yes			
				25min	08:34	8:34				8:34				
				30min	08:39	8:39				8:39			08:44 109/65 HR 92	
				40min	08:49	8:49				8:49			08:54 107/64 HR 91	
				50min	08:59	8:59				8:59				
				60min	09:09	9:09				9:09	Yes			
				75min	09:24	.				9:24				
				80min	09:29	9:29				.				
				90min	09:39	.				9:39				
				100min	09:49	9:49				.				
				105min	09:54	.				9:54				
				120min	10:09	10:09				10:09				
				140min	10:29	10:29				.				
				2.5hrs	10:39	.				10:39				
				160min	10:49	10:49				.				

b(4)

Treatment A=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): Fasting
Treatment B=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): with apple sauce followed 10 minutes later by a light meal
Treatment C=Tyramine rich meal with English Stilton Cheese containing 158 mg free tyramine.

Subject No.	Period	Treatment	Dosing Date	Time Relevant to Dose (Min/hours)	Theoretical Time	Supine BP Actual Time	SBP mmHg	DBP mmHg	PULSE bpm	Blood Sample Actual Time	ECG	Meals	Comments	Released from the CRC
10.0	2	C	16FEB2005	3hrs	11:09	11:09				11:09				
				3.5hrs	11:39	11:39				11:39				
				4hrs	12:09	12:09				12:09	Yes			
				5hrs	13:09	13:09				13:09				
				5.5hrs	13:39	.				.		Yes		
				6hrs	14:09	14:09				14:09	Yes			
				8hrs	16:09	16:09				.	Yes			Yes
	3	A	18FEB2005	Pre Dose		7:19				7:33	Yes			
				0(Dosing)	08:09	.				.				
				5min	08:14	8:14				8:14				
				10min	08:19	8:19				8:19				
				15min	08:24	8:24				8:24				
				20min	08:29	8:29				8:29	Yes			
				25min	08:34	8:34				8:34				
				30min	08:39	8:39				8:39				
				40min	08:49	8:49				8:49				
				50min	08:59	8:59				8:59				
				60min	09:09	9:09				9:12	Yes			
				75min	09:24	.				9:24				
				80min	09:29	9:29				.				
				90min	09:39	.				9:39				
				100min	09:49	9:49				.				
				105min	09:54	.				9:54				
				120min	10:09	10:09				10:09				
				140min	10:29	10:29				.				
				2.5hrs	10:39	.				10:39				
				160min	10:49	10:49				.				
				3hrs	11:09	11:09				11:09				
				3.5hrs	11:39	11:39				11:39				
				4hrs	12:09	12:09				12:09	Yes			
				5hrs	13:09	13:09				13:09				
				5.5hrs	13:39	.				.		Yes		

b(4)

Treatment A=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): Fasting
Treatment B=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): with apple sauce followed 10 minutes later by a light meal
Treatment C=Tyramine rich meal with English Stilton Cheese containing 158 mg free tyramine.

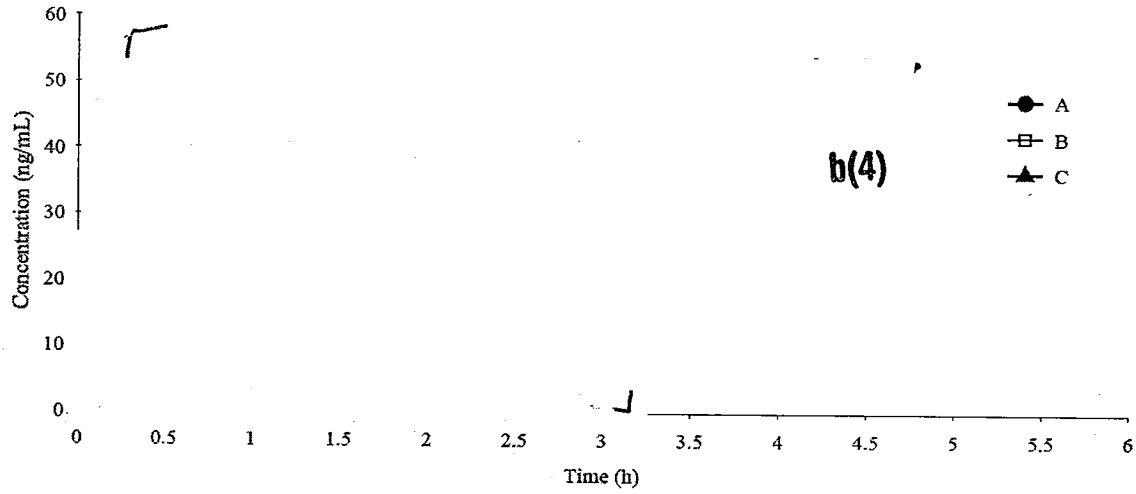
Reviewer Comments

- A single threshold, pressor response was observed at + 25 minutes — compared to pre-treatment of — after the cheese and the SBP is modestly increased at + ——), and + 30 minutes — It is not possible to know if this is a real tyramine threshold, pressor response. It is possible that the single pre-treatment SBP may be a true representative of baseline pressure and may have been inappropriately "low." b(4)

- The plasma tyramine profile on the linear Y axis (upper panel in figure shown below here for subject # 10) appears to peak just before 1 hour. The plasma tyramine profile for Stilton cheese (Treatment C) shows a markedly attenuated Cmax and AUC compared to fasting tyramine. Considering that the threshold, pressor response might be expected around Tmax or soon after Tmax, these data might suggest that this subject's threshold, pressor response was not "real" and related to tyramine.

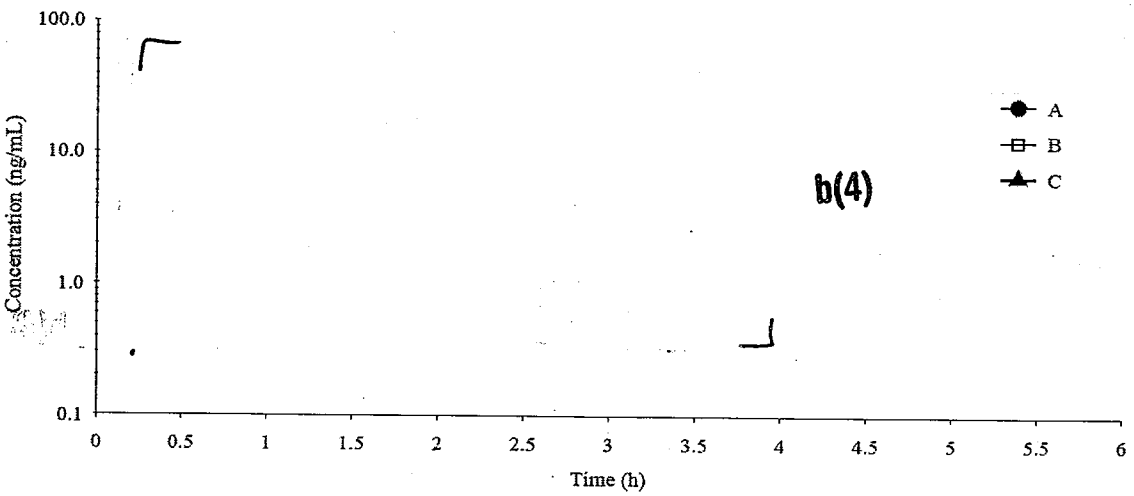
Individual profiles

Subject=10



Individual profiles

Subject=10



Subject No.	Period	Treatment	Dosing Date	Time Relevant to Dose (Min/hours)	Theoretical Time	Supine BP Actual Time	SBP mmHg	DBP mmHg	PULSE bpm	Blood Sample Actual Time	ECG	Meals	Comments	Released from the CRC
10.0	3	A	18FEB2005	6hrs	14:09	14:09				14:09	Yes			
				8hrs	16:09	16:09				.	Yes			Yes
11.0	1	C	14FEB2005	Pre Dose		7:17				7:46	Yes			
				0(Dosing)	08:12	.				.				
				5min	08:17	8:17				8:17				
				10min	08:22	8:22				8:22				
				15min	08:27	8:27				8:27				
				20min	08:32	8:32				8:32	Yes			
				25min	08:37	8:37				8:37				
				30min	08:42	8:42				8:42				
				40min	08:52	8:52				8:52				
				50min	09:02	9:04				9:02			PKTIME 09:02 SP BP TIME 09:04	
				60min	09:12	9:12				9:12	Yes			
				75min	09:27	.				9:27				
				80min	09:32	9:32				.				
				90min	09:42	.				9:42				
				100min	09:52	9:52				.				
				105min	09:57	.				9:57				
				120min	10:12	10:12				10:12				
				140min	10:32	10:32				.				
				2.5hrs	10:42	.				10:42				
				160min	10:52	10:52				.				
				3hrs	11:12	11:12				11:12				
				3.5hrs	11:42	11:42				11:42				
				4hrs	12:12	12:12				12:12	Yes			
				5hrs	13:12	13:12				13:12				
				5.5hrs	13:42	.				.		Yes		
				6hrs	14:12	14:12				14:12	Yes			

b(4)

Treatment A=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): Fasting
Treatment B=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): with apple sauce followed 10 minutes later by a light meal
Treatment C=Tyramine rich meal with English Stilton Cheese containing 158 mg free tyramine.

Subject No.	Period	Treatment	Dosing Date	Time Relevant to Dose (Min/hours)	Theoretical Time	Supine BP Actual Time	SBP mmHg	DBP mmHg	PULSE bpm	Blood Sample Actual Time	ECG	Meals	Comments	Released from the CRC
11.0	1	C	14FEB2005	8hrs	16:12	16:12				.	Yes			Yes
	2	A	16FEB2005	Pre Dose		7:18				7:32	Yes			
				0(Dosing)	08:12	.				.				
				5min	08:17	8:17				8:17				
				10min	08:22	8:22				8:22				
				15min	08:27	8:27				8:27				
				20min	08:32	8:32				8:32	Yes			
				25min	08:37	8:37				8:37				
				30min	08:42	8:42				8:42				
				40min	08:52	8:52				8:52				
				50min	09:02	9:02				9:02				
				60min	09:12	9:12				9:12	Yes			
				75min	09:27	.				9:27				
				80min	09:32	9:32				.				
				90min	09:42	.				9:42				
				100min	09:52	9:52				.				
				105min	09:57	.				9:57				
				120min	10:12	10:12				10:12				
				140min	10:32	10:32				.				
				2.5hrs	10:42	.				10:42				
				160min	10:52	10:52				.				
				3hrs	11:12	11:12				11:12				
				3.5hrs	11:42	11:42				11:42				
				4hrs	12:12	12:12				12:12	Yes			
				5hrs	13:12	13:12				13:12				
				5.5hrs	13:42	.				.		Yes		
				6hrs	14:12	14:12				14:12	Yes			
				8hrs	16:12	16:11				.	Yes			Yes
	3	B	18FEB2005	Pre Dose		7:15				7:36	Yes			
				0(Dosing)	08:12	.				.				
				5min	08:17	8:17				8:17				
				10min	08:22	8:24				8:22				

b(4)

Treatment A=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): Fasting
Treatment B=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): with apple sauce followed 10 minutes later by a light meal
Treatment C=Tyramine rich meal with English Stilton Cheese containing 158 mg free tyramine.

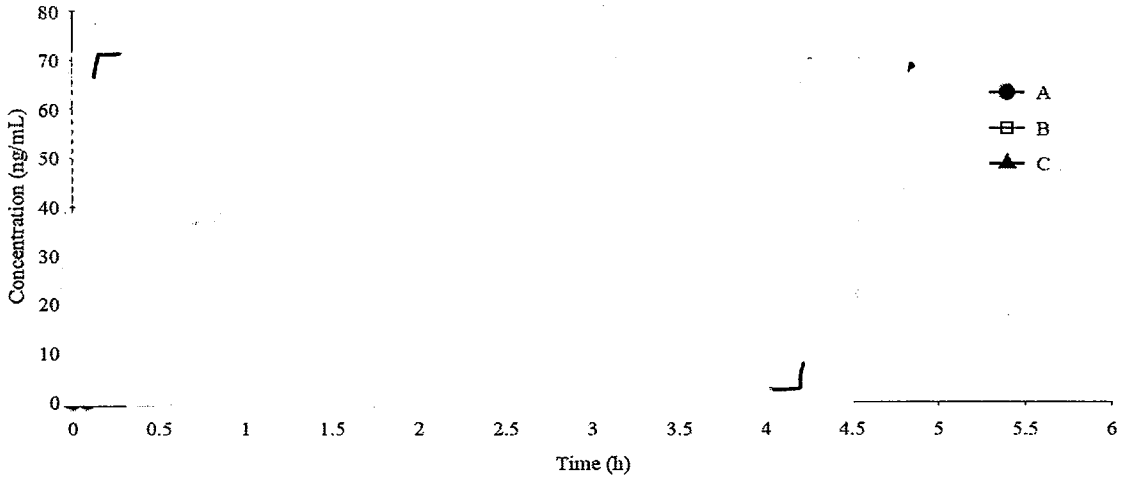
Reviewer Comments

- A single threshold, pressor response was observed at + 30 minutes — compared to pre-treatment of — after the cheese and the SBP is mildly increased at + 25 — and + 40 minutes : — It is not possible to know if this is a real tyramine threshold, pressor response. It is possible that the single pre-treatment SBP may be a true representative of baseline pressure and may have been inappropriately "low." b(4)

- The plasma tyramine profile on the linear Y axis (upper panel in figure shown below here for subject # 11) appears to peak just before 1 hour. The plasma tyramine profile for Stilton cheese (Treatment C) shows a markedly attenuated Cmax and AUC compared to fasting tyramine. Considering that the threshold, pressor response might be expected around Tmax or soon after Tmax, these data might suggest that this subject's threshold, pressor response was not "real" and related to tyramine.

Individual profiles

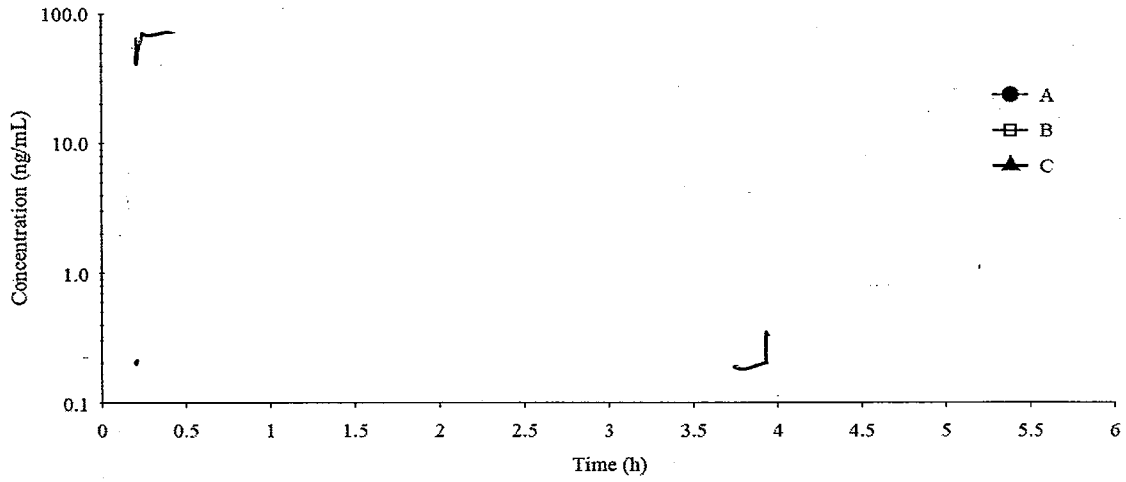
Subject=11



b(4)

Individual profiles

Subject=11



b(4)

Subject No.	Period	Treatment	Dosing Date	Time Relevant to Dose (Min/hours)	Theoretical Time	Supine BP Actual Time	SBP mmHg	DBP mmHg	PULSE bpm	Blood Sample Actual Time	ECG	Meals	Comments	Released from the CRC
13.0	2	B	23FEB2005	6hrs	14:00	14:00				14:00	Yes			
				8hrs	16:00	15:58				.	Yes			Yes
	3	C	25FEB2005	Pre Dose		7:07				7:19	Yes			
				0(Dosing)	08:00	.				.				
				5min	08:05	8:05				8:05				
				10min	08:10	8:10				8:10				
				15min	08:15	8:15				8:15				
				20min	08:20	8:20				8:20	Yes			
				25min	08:25	8:25				8:25				
				30min	08:30	8:30				8:30			08:35-124/80	
				40min	08:40	8:40				8:40			08:45-131/69	
				50min	08:50	8:50				8:50				
				60min	09:00	9:00				9:00	Yes			
				75min	09:15	.				9:15				
				80min	09:20	9:20				.				
				90min	09:30	.				9:30				
				100min	09:40	9:40				.				
				105min	09:45	.				9:45				
				120min	10:00	10:00				10:00				
				140min	10:20	10:20				.				
				2.5hrs	10:30	.				10:30				
				160min	10:40	10:40				.				
				3hrs	11:00	11:00				11:00				
				3.5hrs	11:30	11:30				11:30				
				4hrs	12:00	12:00				12:00	Yes			
				5hrs	13:00	13:00				13:00				
				5.5hrs	13:30	.				.		Yes		
				6hrs	14:00	14:00				14:00	Yes			
				8hrs	16:00	.				.	No			Yes
14.0	1	C	21FEB2005	Pre Dose		7:17				7:19	Yes			

Treatment A=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): Fasting
Treatment B=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): with apple sauce followed 10 minutes later by a light meal
Treatment C=Tyramine rich meal with English Stilton Cheese containing 158 mg free tyramine.

b(4)

Reviewer Comments

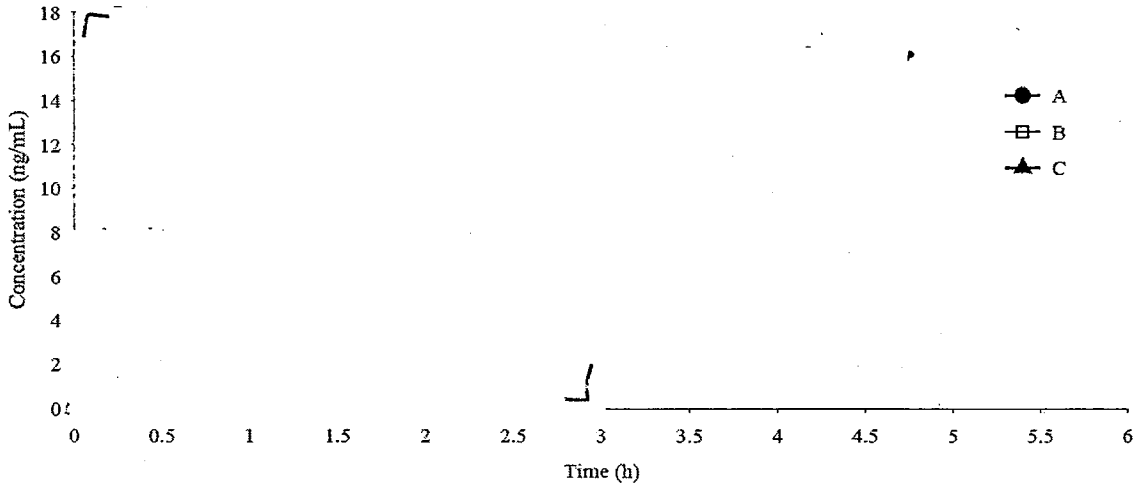
- A single threshold, pressor response was observed at + 30 minutes — compared to pre-treatment of — ter the cheese and the SBP is not increased at + 25 — and minimally increased at + 40 minutes — t is not possible to know if this is a real tyramine threshold, pressor response.

b(4)

- The plasma tyramine profile on the linear Y axis (upper panel in figure shown below here for subject # 13) appears to peak at 1 hour. The plasma tyramine profile for Stilton cheese (Treatment C) shows a markedly attenuated Cmax and AUC compared to fasting tyramine. Considering that the threshold, pressor response might be expected around Tmax or soon after Tmax, these data might suggest that this subject's threshold, pressor response was not "real" and related to tyramine.

Individual profiles

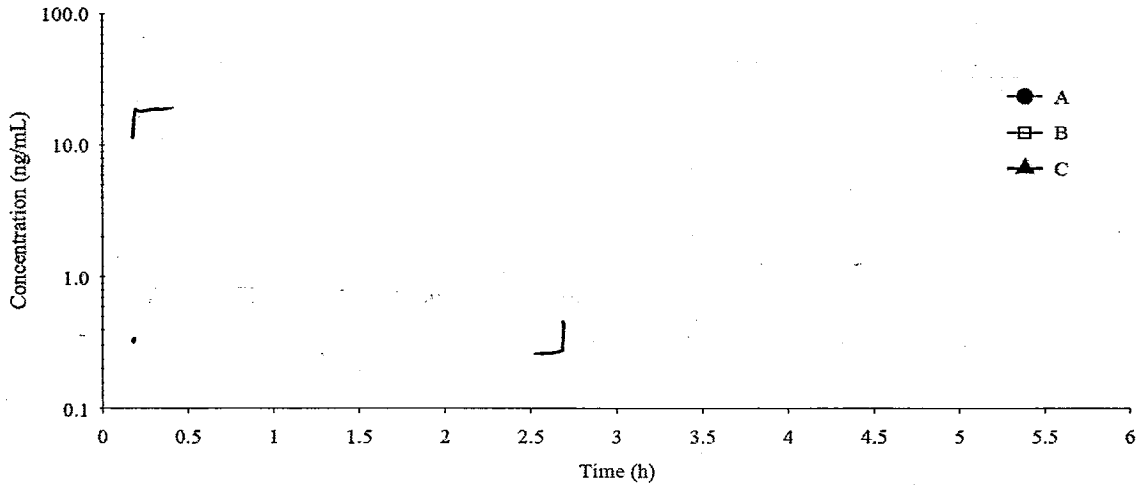
Subject=13



b(4)

Individual profiles

Subject=13



b(4)

Subject No.	Period	Treatment	Dosing Date	Time Relevant to Dose (Min/hours)	Theoretical Time	Supine BP Actual Time	SBP mmHg	DBP mmHg	PULSE bpm	Blood Sample Actual Time	ECG	Meals	Comments	Released from the CRC
4.1	2	B	22DEC2004	30min	08:39	8:39				8:39				
				40min	08:49	8:49				8:49				
				50min	08:59	8:59				8:59				
				60min	09:09	9:09				9:09	Yes			
				75min	09:24	.				9:24				
				80min	09:29	9:29				.				
				90min	09:39	.				9:39				
				100min	09:49	9:49				.				
				105min	09:54	.				9:54				
				120min	10:09	10:09				10:09				
				140min	10:29	10:29				.				
				2.5hrs	10:39	.				10:39				
				160min	10:49	10:49				.				
				3hrs	11:09	11:09				11:09				
				3.5hrs	11:39	11:39				11:39				
				4hrs	12:09	12:09				12:09	Yes			
				5hrs	13:09	13:09				13:09				
				5.5hrs	13:39	.				.		Yes		
				6hrs	14:09	14:09				14:09	Yes			
				8hrs	16:09	16:09				.	Yes			Yes
	3	C	24DEC2004	Pre Dose		7:18				7:22	Yes			
				0(Dosing)	08:09	.				.				
				5min	08:14	8:14				8:14				
				10min	08:19	8:19				8:19				
				15min	08:24	8:24				8:24				
				20min	08:29	8:29				8:29	Yes			
				25min	08:34	8:34				8:34				
				30min	08:39	8:39				8:39				
				40min	08:49	8:49				8:49				
				50min	08:59	8:59				8:59				
				60min	09:09	9:09				9:09	Yes			
				75min	09:24	.				9:24				

Treatment A=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): Fasting
Treatment B=4X50 mg Tyramine HCl Capsule (total of 200mg equal to 158 mg free tyramine): with apple sauce followed 10 minutes later by a light meal
Treatment C=Tyramine rich meal with English Stilton Cheese containing 158 mg free tyramine.

Subject No.	Period	Treatment	Dosing Date	Time Relevant to Dose (Min/hours)	Theoretical Time	Supine BP Actual Time	SBP mmHg	DBP mmHg	PULSE bpm	Blood Sample Actual Time	ECG	Meals	Comments	Released from the CRC
4.1	3	C	24DEC2004	80min	09:29	9:29				.				
				90min	09:39	.				9:39				
				100min	09:49	9:49				.				
				105min	09:54	.				9:54				
				120min	10:09	10:09				10:09				
				140min	10:29	10:29				.				
				2.5hrs	10:39	.				10:39				
				160min	10:49	10:49				.			RECHECKED 10:52 BP 137/69 P73	
				3hrs	11:09	11:09				11:09				
				3.5hrs	11:39	11:39				11:39			REPEATED 11:40 SP 143/75 P79	
				4hrs	12:09	12:09				12:09	Yes			
				5hrs	13:09	13:09				13:09				
				5.5hrs	13:39	.				.		Yes		
				6hrs	14:09	14:09				14:09	Yes			
				8hrs	16:09	16:07				.	Yes			Yes

b(4)

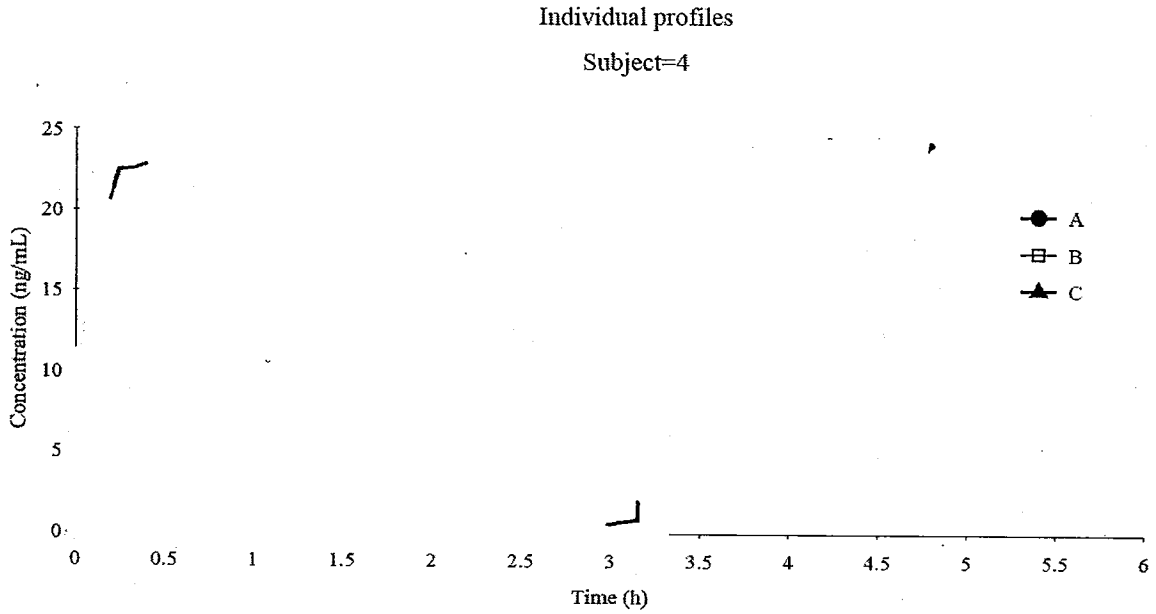
b(4)

Reviewer Comments

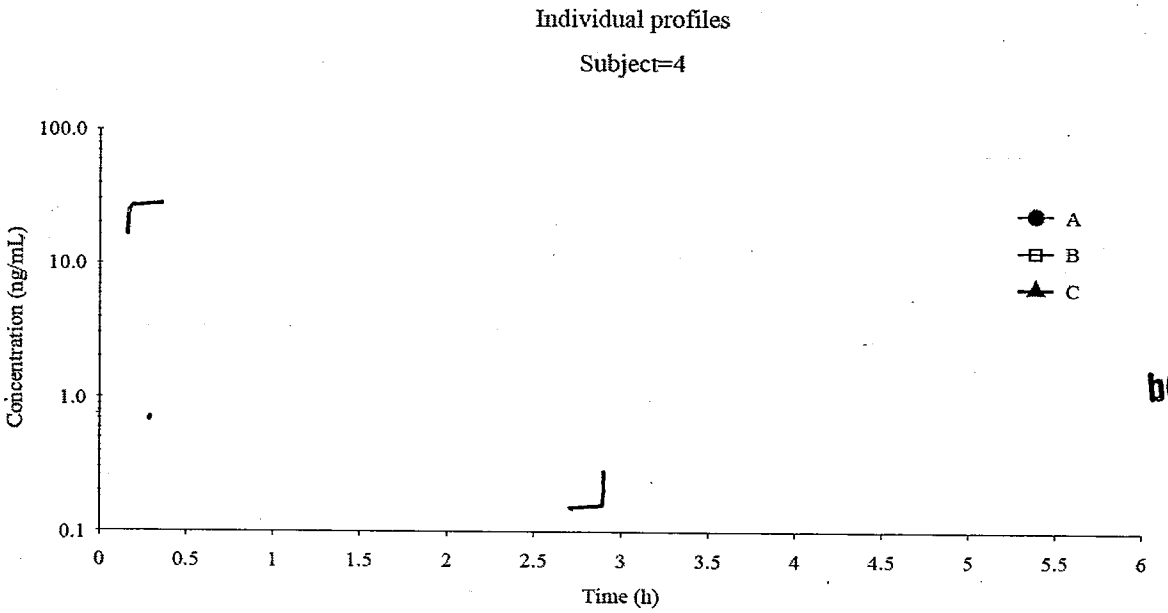
- Multiple threshold, pressor responses were observed at + 160 minutes — compared to pre-treatment of — + 210 minutes —, + 300 minutes — and + 480 minutes — after the tyramine-rich cheese. Because there were no BP measurements a few minutes before or after each of these threshold, pressor increases, it is difficult to know if there was a sustained increased SBP at each time. Furthermore, it is not known nor expected that one would experience multiple threshold, pressor responses at different

times over an extended period after ingesting tyramine-rich cheese. Overall, it is difficult to know if these increases are "real" tyramine threshold, pressor response.

- The plasma tyramine profile on the linear Y axis (upper panel in figure shown below here for subject # 4) appears to peak at 1.5 hours. The plasma tyramine profile for Stilton cheese (Treatment C) shows a markedly attenuated Cmax and AUC compared to fasting tyramine. Considering that the threshold, pressor response might be expected around Tmax or soon after Tmax, these data might suggest that this subject's multiple threshold, pressor response were not "real" and related to tyramine stimulation.


Individual profiles
Subject=4
Concentration (ng/mL)
25
20
15
10
5
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
Time (h)
A
B
C

b(4)


Individual profiles
Subject=4
Concentration (ng/mL)
100.0
10.0
1.0
0.1
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
Time (h)
A
B
C

b(4)

5. LABELING SUPPLEMENTS FOR NDA 21641 FOR RASAGILINE/AZILECT

This review for the tyramine challenge study NDA submission will also deal with several other labeling supplements that have been submitted by the sponsor under NDA 21641 for rasagiline/AZILECT.

The following briefly describes the subject of the labeling supplement submission and my review comments.

1-Feb-07 **S-002** Prior Approval Supplement (PAS): Provided proposed labeling for review in response to the Division's letter, dated October 6, 2006, requesting a change in the Information for Patients subsection of the product labeling related to reports of compulsive behavior with Parkinson's disease medications.

Reviewer Comments

- The sponsor has submitted labeling language for compulsive behavior. The DNP has inserted language regarding this issue into a revised AZILECT label in PLR format and has negotiated this with the sponsor. I concur with the negotiated label revision.

11-May-07 **S-003** PAS: Provided a response to the Division's letter, dated December 20, 2006, requesting a change in Warnings section of the product labeling related to co- administration of Azilect with a catechol-o-methytransferase (COMT) inhibitor.

Reviewer Comments

- The sponsor has noted that it does not believe such a warning for a COMT inhibitor is appropriate because it expects that the tyramine challenge study will show that AZILECT is a "selective" MAO-B inhibitor and requested that this issue be delayed until the tyramine challenge study has been submitted and reviewed. Based upon the relative selectivity of AZILECT for MAO-B, I believe that it is not necessary to restrict patients taking a COMT inhibitor from also taking AZILECT. COMT inhibitors are not ordinarily used with non-selective MAO inhibitors.

1-Jun-07 **S-004** PAS: Provided proposed labeling for review. The submission is in response to the Division's letter, dated March 27, 2007, requesting a change in the Precaution section of the product labeling to reflect class labeling related to the increased risk of melanoma in Parkinson's disease patients.

Reviewer Comments

- The sponsor has submitted labeling language for a possible risk of melanoma. The DNP has inserted language regarding this issue into a revised AZILECT label in PLR format and has negotiated this with the sponsor. I concur with the negotiated label revision.

26-Oct-07 **S-005** PAS: Provided revised labeling based upon the information submitted in the September 28, 2007 Response to FDA. Summary of changes include the change of red wine listed as a beverage to avoid to red wine listed as an acceptable beverage in the tyramine table. One mention of red wine in the WARNINGS section and two mentions in the PRECAUTIONS were also deleted.

Reviewer Comments

- Previously, the AZILECT label had included a dietary tyramine restriction from using red wine. Although red wines should be avoided because of the possible risk of a hypertensive, tyramine-induced reaction from tyramine-rich red wine, this restriction is no longer applicable to the AZILECT because standard tyramine dietary restrictions in the label are being deleted in view of the relatively selective nature of approved doses of AZILECT for MAO-B inhibition.

19-May-08 **S-007** PAS: Supplement submitted in response to a comment communicated to Teva from the clinical pharmacology reviewer for this NDA that a proposal for updating the labeling according to the results of the Phase IV commitment dose proportionality study should be made.

Reviewer Comments

- Clinical Pharmacology has reviewed this supplement and provided their comments.

06-Feb-09 S-008 PAS: Provided CSR to satisfy Phase IV commitment for tyramine challenge study. Also provided for labeling change pertaining to MAO-B selectivity. Provided safety update --The efficacy supplement with a due date of 12/9/09

Reviewer Comments

- This labeling supplement is the main subject of this review that has outlined my views on the relatively selectivity of AZILECT for MAO-B inhibition and the need to revise the AZILECT label on this topic.

Supp 10:
10-Apr-09 CBE: provides for the following safety updates to the product labeling:
o Addition of information in Adverse Reactions section relative to postmarketing reported cases of serotonin syndrome
o Addition of information in Adverse Reactions section relative to postmarketing cases of elevated blood pressure, including one report of hypertensive crisis, with ingestion of unknown amounts of tyramine-rich foods
o Addition of information in Adverse Reactions section relative to a postmarketing case of elevated blood pressure in a patient taking AZILECT and ophthalmic tetrahydrozoline hydrochloride
o Addition of Overdosage information reported in Postmarketing Periodic Safety Report

Reviewer Comments

- Information about these post-marketing experiences/reports have been incorporated into a revised label that has been negotiated with the sponsor.

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

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

/s/

LEONARD P KAPCALA
12/09/2009

GERALD D PODSKALNY
12/09/2009