

MEMORANDUM

DATE: July 23, 2005

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-641

SUBJECT: Recommendation for action on NDA 21-641, for the use of Rasagiline mesylate in the treatment of patients with Parkinson's Disease (PD)

NDA 21-641, for the use of Rasagiline mesylate, a presumed selective MAO-B inhibitor, in the treatment of patients with Parkinson's Disease (PD), was submitted by TEVA Pharmaceuticals, LTD., on 9/5/03. The Agency issued an Approvable letter on 7/2/04, which included questions related to the following issues:

Tyramine Studies

The sponsor had presented data from several studies designed to document that rasagiline was selective for MAO-B at the recommended daily dose of 1 mg, and that its use at this dose was not associated with hypertensive crises in the face of ingestion of foods high in tyramine content (so called "cheese" reaction). However, we had not been persuaded that the absence of the potential for such a reaction without a restricted diet had been conclusively demonstrated.

Briefly, the sponsor had performed one formal tyramine challenge study which ostensibly showed no worrisome reactions at 1 mg, but we found this study unreliable because many subjects did not show an increase in blood pressure even at the highest dose of tyramine administered (800 mg), which was not consistent with the experience seen in numerous other such studies with other compounds. Further, there were small numbers of subjects, no elderly subjects, and the blood pressure criteria used were unconventional.

The sponsor submitted the results of three other challenge studies, in which the tyramine was not given in the fasted state (the typical approach in challenge studies) but was given mixed with food. The sponsor had provided no evidence that the amount of tyramine absorbed when given in this fashion approximated the amount of tyramine absorbed when given as a meal with high tyramine content food. Further, it was clear from the literature that the bioavailability of tyramine from a capsule when given with food was much less than when it is given in the fasted state, making the results obtained (which were negative) questionable.

Other findings raised concerns about the selectivity of a 1 mg dose for MAO-B. In PRESTO (a pivotal study in which rasagiline was given in combination with levodopa), three patients receiving a 0.5 mg dose had tyramine reactions (none of the 19 patients who received the 1 mg dose in TEMPO, a pivotal monotherapy study, had such a reaction), raising questions about an interaction with levodopa. Again, the decreased bioavailability of tyramine when given with food also raised questions about the adequacy of the timing of the blood pressure monitoring in these studies; that is, the frequency of blood pressure monitoring was relatively infrequent after two hours, when tyramine's delayed Cmax might have been expected to have occurred.

For these reasons, we asked the sponsor to perform a thorough, state of the art, tyramine challenge study.

Melanoma

We had concluded that the data, taken as a whole, suggested that use of rasagiline might have been associated with an increased risk for melanoma.

Specifically, we had observed that the rates of melanoma occurrence in the NDA database exceeded that which would have been expected based on comparisons to two external databases; the SEER database and the American Academy of Dermatology (AAD) database.

Even with underreporting in the SEER database, the number of tumors seen in the NDA exceeded the number expected based on the SEER data. However, we acknowledged that patients in the SEER database had not been actively monitored for melanoma (as had patients in the NDA database after a certain point in time); however, patients in the AAD database had been actively screened. A comparison of the patients whose tumor had been detected on the first screening visit in the NDA (in the AAD database, patients were screened once) with the AAD database revealed a 2.5 relative risk for rasagiline-treated patients.

For these reasons, we asked the sponsor to provide a dose response analysis for melanoma, more formal analyses of Study EP002 (a prospective study in PD patients who did not receive rasagiline treatment, which the sponsor asserted demonstrated that patients with PD have an increased incidence of melanoma), and a pooled analysis of PRESTO and TEMPO, each of which had an initial placebo controlled randomized phase, followed by a phase in which placebo patients were switched to active drug, while the original rasagiline-treated patients were continued on active drug [delayed start phase], and then an open-label phase. We had concluded that these concerns would not preclude ultimate approval, but that a statement in the Warnings section of labeling would need to be included, and that the sponsor should perform a large controlled trial to further investigate this issue in Phase 4.

Other issues were raised in the Approvable letter, including requests for additional analyses of EKG data, of adverse events related to Flu Syndrome, of vital sign and lab data, of selected adverse events leading to discontinuation, and a request for post-marketing surveillance for rhabdomyolysis. Also, in draft labeling, we had included a statement in the Warnings section about the concomitant use of antidepressants and rasagiline, based on a potential risk of serotonin syndrome (a similar statement appears in the labeling for selegiline); the sponsor addressed this issue as well. In addition, there were numerous CMC requests, a request for additional analyses of the 2-year carcinogenicity study in rats, and an assessment of several potentially genotoxic impurities that might form during the synthesis of rasagiline. We also asked for additional data pertaining to the adequacy of the rabbit embryo-fetal development study. Additional packaging and biopharmaceutics questions were raised.

The sponsor responded to the Approvable letter in a submission dated 11/4/04. An amendment to the application was submitted on 5/24/05, which resulted in an extension of the PDUFA due date to 8/4/05. The submission has been reviewed by Dr. Lisa Jones, safety team medical reviewer, Dr. Len Kapcala, neurology medical reviewer, Dr. Tristan Massie, statistician (carcinogenicity data), Dr. Paul Roney, pharmacologist, Dr. Lois Freed, supervisory pharmacologist, Dr. William C. Timmer, chemist, Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics, and Dr. John Feeney, neurology drugs team leader. The review team has concluded that the application should not be approved at this time, primarily because of concerns related to the occurrence of melanoma, and the inadequate characterization of the response to tyramine at the recommended 1 mg dose.

Melanoma

As noted earlier, we asked the sponsor to provide a dose response analysis for the occurrence of melanoma, demographic and age related analyses of EP002, and further analyses of the melanoma data in PRESTO and TEMPO.

Dose-Response Analyses

Dr. Jones has calculated the rate of melanoma cases/100,000 patient years of exposure, excluding cases that occurred prior to drug exposure. In these analyses, patients' data could be included in multiple dosing cells. That is, if a patient received varying doses of rasagiline, their experience at each dose they received was included in the denominators. Further, in these analyses, the patient's modal dose was used as the dose at which the tumor occurred (that is, for the numerator data), as opposed to the actual dose the patient might have been receiving at the time the tumor was diagnosed. Dr. Jones's Table 4 displays the results of these analyses:

Total tumors (invasive and in situ; per 100,000 pt-years)

	Pbo	0.5mg	1mg	2mg
Number of cases	1	2	11	4
Cases/100,000 Pt-years	238	677	720	738

EP002 Analyses

This was a study performed in 31 North American centers, in which investigators were instructed to ask all PD patients not exposed to rasagiline if they wished to be screened for melanoma. If they agreed to participate, they were assessed by a neurologist and a dermatologist. The dermatologist obtained a detailed history, and performed a detailed dermatological examination. Although the sponsor included tumors described by the patients for the two years prior to their enrollment in EP002, Dr. Jones used in her analyses only those tumors detected by the dermatologist in his or her examination. This permitted a fair comparison to the risk for melanoma as seen in the AAD database, which was the Agency's primary intention.

Dr. Jones has provided the following comparisons in her Table 10 (the Expected number of tumors is obtained from the AAD data):

Tumors	Observed	Expected	O/E	95% CI
Invasive	4	3.3	1.2	0.3, 3.1
In Situ	20	1.2	16.7	10.2, 25.7
Total	24	4.5	5.3	3.3, 7.9

As Dr. Jones points out, there are some differences between the patients in Study EP002 and those included in the AAD screening study. First, the AAD study was done between 1992-1994, and EP002 was conducted between 1/03 and 9/04; as she notes, melanoma rates are increasing significantly over time, so any increase in the estimate of the rate obtained by comparing EP002 data to the AAD data may be confounded by this secular trend. Further, EP002 included patients from Canada (about 20%), whereas the AAD study included only US patients. Because melanoma rates decrease with increasing latitude, this too could have an effect on the interpretation of the comparison. Further, in the AAD study, confirmatory records for only about 72% of lesions suspicious for melanoma were returned for examination. These factors may contribute to either an over or under-estimate of the O/E ratio, making the conclusion that PD itself is a major contributing risk factor for melanoma somewhat uncertain.

Dr. Jones has also provided in her review the comparison she previously made between the experience in the NDA dataset for rasagiline-treated patients and the AAD data:

Tumors	Observed	Expected	O/E	95% CI
Invasive	4	1.5	2.6	0.72, 6.74
In Situ	6	0.59	10.2	3.7, 22.1

There seemed to be no important difference in the risk of either invasive or in situ melanoma in patients with or without concomitant levodopa treatment.

The discrepancy between the risk for invasive compared to in situ tumors is difficult to explain. According to Dr. Jones, it is likely that different types of patients were recruited into the two different studies. Specifically, patients recruited into the AAD study were recruited via advertising in the local media, and 80% did not have a regular dermatologist, 60% had never had their skin examined by a doctor, and 51% said that they never would have had a dermatologic examination except for the free screening provided by the AAD study. In contrast, the patients enrolled in EP002 were recruited by their medical care providers, which presumably is evidence that they had access to better health care, which suggests to Dr. Jones that these patients might have been more likely to have had suspicious lesions removed prior to enrollment in the study. This, and the presumably greater skin surveillance in this latter cohort, may have contributed to a relative decrease in the number of invasive compared to in situ tumors in the EP002 patients.

Delayed vs Immediate Start Analyses

As noted above, both PRESTO (adjunctive; 0.5 mg, 1 mg, or placebo) and TEMPO (monotherapy; 1 mg, 2 mg, or placebo) studies treated patients with randomized study drug for 6 months, after which patients initially randomized to placebo were treated in a double-blind fashion with active drug for another 6 months (PRESTO placebo patients were randomized to one of the above rasagiline doses; TEMPO placebo patients received 2 mg of rasagiline). Finally, an open-label period followed these two phases.

A total of 17 tumors were detected in these two studies. A total of 15 of these tumors occurred in the patients initially randomized to rasagiline (Immediate Start), with 2 occurring in the patients originally randomized to placebo (Delayed Start).

In the Immediate Start group, the rate of melanoma was 15/1345 Pt-yrs, or 11.2 tumors/1000 PYs of exposure. In the Delayed Start group, the rate was 2/557 PYs, or 3.6 tumors/1000 PYs., with overlapping 95% CIs.

In an attempt to examine the question of any potential latency to tumor onset (that is, is there an increase in tumor occurrence with increasing duration of exposure to rasagiline), Dr. Jones provides the following data table:

Study Group	Month of tumor detection from time of first rasagiline dose				
	0-6	6-12	12-18	18-24	>24
PRESTO Immed	3 (1%)	2 (0.6%)	1 (0.3%)	0	0
PRESTO Delay	1 (0.6%)	0	0	0	0
TEMPO Immed	1 (0.4%)	0	2	0	6 (2%)
TEMPO Delay	0	0	0	0	1(.7%)

As can be seen, there is a considerable discrepancy in the times at which the tumor was first detected between the two studies. As pointed out by Dr. Jones, active screening for melanoma in the development program began between 10-12/01. TEMPO was well underway at that time (as Dr. Jones points out, the open label phase began in 1999). The dates of conduct of PRESTO were 12/00-1/03, and between 42-44% of PRESTO patients had a dermatologic screening examination at baseline. Therefore, as Dr. Jones notes, the timing of the initiation of active screening for tumors confounds the interpretation of the differences in the duration epoch in which tumors were diagnosed in the two studies.

In addition to these analyses, the following chart displays the total incidence (by duration epoch) of tumors in these trials:

	Year of tumor diagnosis from time of first dose				
	0-.5	.5<1	1<2	2<3	3+
Tumors/100PYs	0.7	0.9	0.4	0.3	1.1
PYs	606.4	458.9	563.4	374.4	642.9
CI	(0.2,1.5)	(0.3,2)	(0.06,1.1)	(0.02,1.2)	(0.5,2)

Tyramine Analyses

As noted above, we had previously noted numerous deficiencies in the sponsor's attempts to document that, at a 1 mg daily dose of rasagiline, there are no untoward hypertensive events in the face of a tyramine challenge, and that, therefore, this dose could be approved without dietary restrictions. As a result,

we had required the sponsor to perform an adequate tyramine challenge study prior to approval.

The first issue raised in the Approval letter noted that we had concerns about the validity of the one fasting tyramine study (the Paris study) because many subjects did not experience a blood pressure elevation at the maximum administered tyramine dose of 800 mg (in fact, the tyramine capsules used in this study were used in the sponsor's three other challenge studies as well). In our experience, based on numerous tyramine challenge studies in other NDAs, all or almost all subjects do experience a blood pressure response to this (or lower) dose(s).

The sponsor cites several literature reports that, in their view, suggest that a reasonable number of normal subjects actually do not experience a blood pressure response at these high tyramine levels. However, the articles do not document the numbers of unscreened subjects who actually do not experience a blood pressure response to tyramine doses of 800 mg or greater (some articles describe various exclusion criteria for tyramine challenge studies, in which subjects who respond to either low or high doses of tyramine are excluded from the specific study, but only one report describes the number of subjects who did not respond to a tyramine dose of 600 [not 800] mg; in that study 3/24 subjects did not respond to this dose). As Dr. Kapcala describes, of a total of 105 subjects of which we are aware in various NDAs, none required a tyramine dose of > 700 mg to experience a response. Again, as he points out, the sponsor has not made any attempt to document that the tyramine that they used in their studies had an appropriate degree of bioavailability.

As noted earlier, the sponsor performed three other tyramine challenge studies. In all of these studies, tyramine capsules were given in close temporal proximity to a meal.

In Study 132, 20 patients with PD and receiving concomitant levodopa and doses of rasagiline of 1 mg, 2 mg, or placebo, received doses of tyramine of 25, 50, and 75 mg, on Days 22, 23, and 24 respectively, and a 75 mg dose again on Day 70 (study end). No patients at the 1 mg dose experienced a blood pressure response, and 2 patients at the 2 mg dose did reach blood pressure criteria for a response (one each at 25 and 75 mg tyramine dose).

In the TEMPO study, 57 patients with PD who had been on rasagiline 1 mg, 2 mg, or placebo for 6 months received tyramine doses of 75 mg; no patient had a pressor response, although two patients at the 2 mg dose had elevations just below the criteria. Dr. Kapcala has performed some additional analyses on this study, and has shown that there is a (slight) dose related increase in the mean maximal systolic pressure after a 75 mg dose of tyramine (137, 148, and 153 mm Hg in the placebo, 1 mg, and 2 mg dose groups, respectively), and a similarly ordered increase in the mean maximal systolic pressure increase. Finally, he

noted an increase in the proportion of patients who experienced a systolic pressure increment of at least 30 mm Hg in response to the tyramine challenge (6%, 21%, and 16% in the placebo, 1 mg, and 2 mg dose groups, respectively).

In the PRESTO study, 55 patients with PD and concomitant levodopa receiving either rasagiline 0.5 mg, 1 mg, or placebo were challenged with a tyramine dose of 50 mg. No patients at the 1 mg dose reached pressor criteria, although 1 placebo patient did (and 3 more placebo patients met pressor criteria for 3 of 4 measurements, but not 3 consecutively), and 3 patients at the 0.5 mg dose did.

As noted above, a primary concern of ours was that the tyramine administered with, or in close temporal proximity to, meals, in the three other challenge studies might have resulted in markedly decreased bioavailability compared to a similar dose given fasting. In addition, we had no information about the availability of tyramine given in such a way compared to a similar amount of tyramine in a meal with tyramine containing food.

There is evidence from the literature that a given dose of tyramine given in the fasting state results in a much greater and earlier C_{max} compared to the same dose given with food. The sponsor argues that the addition of tyramine to applesauce (which it was in one of the challenge studies) could not have altered its bioavailability because applesauce did not alter the bioavailability of several other drugs, but they do not address the specific effects of applesauce on tyramine BA. More importantly, they do not address the larger question of tyramine's BA when given with a meal (when it was given with applesauce, it was also given in proximity to a larger meal).

Further, Dr. Kapcala cites a study published in 1989 by Berlin et al (Clin Pharm Ther, 46:344-351, 1989) that demonstrates that patients receiving treatment with a drug associated with clear MAO-A inhibition (TSF of about 5) are not very sensitive to tyramine administered with food. This would mean that even if rasagiline was associated with a TSF of 5, subjects might have need doses of tyramine of at least 150 mg to demonstrate a response; in these three challenge studies, subjects received doses of 50 or 75 mg of tyramine. Clearly, it is possible then that the study conditions were not suitable to detect an effect if there was one.

Finally, because BP measurements were done frequently only up to 2 hours post-meal, we have little confidence that the maximum effect of the tyramine was adequately captured.

Blood pressure monitoring in the PRESTO study

In the PRESTO study, patients monitored their blood pressures at baseline, during the third week of the study, and during the last week of the trial. Blood pressure readings were to be performed before and at 45 and 90 minutes after

their main meal of the day for 7 days, during the time periods described (recall that in PRESTO, patients receiving concomitant levodopa were randomized to either placebo, rasagiline 0.5 mg, or rasagiline 1 mg/day).

According to the sponsor, over 65,000 BP measurements were recorded, and the proportion of patients in each group who experienced an increase in systolic BP > 30 mm Hg was equal across the groups. However, as described by Dr. Kapcala, by protocol, for various reasons, about 20,000 BP measurements were excluded from the formal analyses, and in actuality, the analyses performed by the sponsor were based on approximately 14-15,000 BP measurements/treatment group.

By protocol, BP measurements were to be excluded from analysis for the following reasons: 1) data without subject ID number, 2) measurements taken at visits other than baseline, Week 3, or Week 26, 3) measurements taken during meals, 4) measurements taken > 1 hour before the meal, 5) measurements taken within 15 minutes after the meal, 6) measurements taken > 180 minutes after the meal, 7) measurements taken without a recorded meal start or stop time, 8) measurements taken with "illogical" meal schedule information, 9) measurements considered "non-physiological"; e.g., pulse pressure < 15 mm Hg, systolic > 260 or < 60 mm Hg, diastolic > 140 or < 40 mm Hg, 10) duplicate measurements taken within 10 minutes of each other showed extreme differences.

Dr. Kapcala has presented the distribution of the reasons for the exclusion of BP data in this study.

The distribution of any given reason for excluding BP measurements across treatment groups was relatively equal, although the number of records excluded for particular reasons varied widely. For example, the largest number of measurements excluded in all treatment groups was for records that did not record meal times; about 3500-4500 records were excluded from each treatment group for this reason. The next most frequent reasons for excluding data were "excessive records in either the first or second post-meal period"; about 650-750 measurements were excluded for this reason across groups (by protocol, only 1 measurement, or acceptable duplicate, was permitted in either of the two post-meal intervals; 1-70 minutes, and 71-180 minutes), and records recorded > 60 minutes prior to the meal (about 600-800 records excluded across treatment groups). About 400 records in each treatment group were excluded because they were obtained during the meal. About 220-290 measurements were excluded from each treatment group for "non-physiologic" measurements, although apparently none were excluded for a systolic BP of >260 mm Hg.

Although the sponsor asserts that these 14-15,000 measurements/treatment group are the relevant data, Dr. Kapcala points out that many of these measurements were either baseline, or pre-meal measurements. These readings have value (primarily serving as reference values), but, as he rightly

points out, the primary measurements of interest were those taken on treatment and post-meal. In this latter category, there were about 5-6,000 readings/treatment group. This is not to point out a flaw in the sponsor's study, but merely to highlight the fact that there were far fewer on-treatment, post-meal measurements than appear to be the case based on the sponsor's presentation (also, of course, the number of patients in whom these measurements were taken was about 140-150/treatment group).

Dr. Kapcala asked the sponsor to perform a number of additional analyses. These analyses are based on the 5-6,000 post-meal BP measurements/treatment group described above.

First, he asked the sponsor to calculate the difference in the proportion of patients who met BP outlier criteria at baseline and on treatment for two outlier criteria: 1) increase in systolic BP > 30 mm Hg to > 140 mm Hg, and 2) increase in systolic BP > 30 mm Hg to > 180 mm Hg; the results are presented below:

Criteria	Pbo	0.5 mg	1 mg
1	7.7%	12.2%	5.3%
2	1.4%	2.0%	3.0%

Second, he asked the sponsor to calculate the difference in the rate of outlier measurements (# of outlier increments/# of measurements) at baseline and on treatment using the same outlier criteria; the following chart displays the results:

Criteria	Pbo	0.5 mg	1 mg
1	.36%	.35%	.20%
2	-.02%	.17%	.06%

As Dr. Kapcala notes, about 95% of the post-meal BP measurements were collected within 150 minutes of the meal, and only about 2-3% were collected beyond 180 minutes. As he notes, at least one article in the literature documents that peak pressure response after a meal to which tyramine was added occurred at 150 minutes or later in 83% of subjects, and after 180 minutes post-meal in 65% of cases. These data suggest that, again, blood pressure monitoring in this study may have been inadequately performed. Further, although this study was done without dietary tyramine restrictions, we have no information about how many, if any, of the meals studied, contained a high tyramine content.

EKG Analyses

Dr. Jones has reviewed the EKG interval data from the adjunctive and monotherapy studies. She finds no evidence that rasagiline has an important effect on the typical EKG intervals, and I agree. I do not believe that a thorough QT study needs to be performed in Phase 4.

Blood Pressure Analyses

As Dr. Jones notes, the sponsor has presented pooled data from 6 Phase 1 studies (4 were placebo controlled) in healthy subjects to examine the question of whether there are significant changes in blood pressure timed appropriately to dosing. There were a total of 60 subjects exposed to rasagiline in these studies, and 33 subjects exposed to placebo. Two studies (a total of 24 subjects on rasagiline) evaluated single doses from 1 mg to 20 mg, and two studies (a total of 36 rasagiline subjects) examined multiple doses of 1, 2, 5, or 10 mg/day for up to 25 days. Of the 60 subjects exposed to rasagiline, 54 (90%) did not experience any episodes of orthostatic hypotension; 6 (10%) did. A total of 11 of the placebo patients (33%) met criteria for orthostatic hypotension. In the rasagiline treated subjects, there did not appear to be any dose response, or any obvious difference between single and multiple doses.

Dr. Jones has concluded that these data, though somewhat reassuring, do not adequately address the question, because the data have been pooled over very different study conditions, and the subjects did not have PD. She believes, however, given the reassuring nature of the data as presented, that a more definitive study can be done in Phase 4. I agree that it would be valuable to obtain well timed BP data in PD patients, and I also agree, given the results of these Phase 1 analyses, as well as the overall experience in the PD population in the NDA, that a more definitive study can be performed in Phase 4.

Flu Syndrome Analyses

As Dr. Jones describes, there is no clear evidence that rasagiline use is associated with a distinct flu-like syndrome, although some analyses demonstrate a slight increase in the number of patients who had complaints referable to specific joints (dose response for complaints referable to the hip, knee, and elbow in the monotherapy study and an increased incidence of complaints referable to the shoulder, hip, knee, and unspecified joints in the 1 mg vs placebo group in the adjunctive studies).

Laboratory and Vital Sign Analyses

There were no significant changes in laboratory values, and a very slight increase in the mean maximal decrease in standing systolic BP in the 2 mg dose

group (16.2 mm Hg) compared to that seen in the 1 mg and placebo groups (about 14 mm Hg) in the monotherapy study, and a slight increase in the mean maximal postural change (supine-standing systolic and diastolic BP) from placebo to 1 mg (10.5 mm Hg and 11.9 mm Hg for systolic BP, respectively, and 7.4 mm Hg and 8.3 mm Hg for diastolic BP, respectively).

Attribution of Discontinuations Analyses

Analyses of the reasons for discontinuations for the 7% of patients for whom this was unknown at the time of the original NDA review produced no new conclusions.

Rhabdomyolysis/Phase 4 Request

The sponsor has proposed specific criteria for the identification of cases that would qualify for submission as 15 day alert reports (there is apparently no universally agreed upon useful operational definition of rhabdomyolysis). Dr. Jones in general agrees with the sponsor's criteria. However, one criterion is a 10 fold increase in the CPK from baseline by itself (other criteria include any elevation in CPK and various symptoms). Dr. Jones recommends that the CPK increase without symptoms should be lowered to a 5 fold increase, and I agree.

Antidepressants/Rasagiline and Serotonin Syndrome

As noted above, we had included in the draft label a Warning Statement about the concomitant use of rasagiline and antidepressants, based on concerns for the occurrence of serotonin syndrome (which has been reported for the concomitant use of selegiline and antidepressants). In response, the sponsor examined their data to determine if any such cases had occurred in the NDA database.

No cases suggestive of serotonin syndrome had occurred, but only about 250 patients received concomitant antidepressant treatment with rasagiline, and, as noted by Dr. Jones, most of the antidepressant use was at doses lower than the labeled therapeutic doses for these drugs (the use of some antidepressants, for example, fluoxetine, was prohibited in these studies). The absence of any recorded cases of serotonin syndrome in the database, therefore, cannot be taken as reliable evidence that the concomitant use of antidepressants and rasagiline is not associated with a risk of serotonin syndrome, and Dr. Jones concludes that the Warnings statement should stand, and, indeed, should be strengthened to inform prescribers about the shortcomings of the data. I agree.

Pharmacology Comments

In the Approvable letter, we asked the sponsor to submit analyses of the low and mid-dose groups in the rat carcinogenicity data. They have done so, and on

review a significantly positive dose trend was found for benign ovarian tumors. A single malignant Sertoli cell tumor was noted in a control female, and, according to Dr. Freed, all of these tumor types may be combined. When this is done, there is no longer a significant trend.

We had also asked the sponsor to limit the presence of several potential genotoxic impurities (rasagiline is a mesylate salt) to $1 \mu\text{g/day}$. The sponsor has agreed to do so for the $1 \mu\text{g/day}$ potential impurities in the drug substance, but can only, at this time, limit the one impurity in the drug product (which is known to be genotoxic) to $1 \mu\text{g/day}$. At this limit, the amount of this impurity in the drug product will be substantially below the acceptable daily limit of $1 \mu\text{g/day}$ micrograms/day. Drs. Roney and Freed find this acceptable, as do I.

Additionally, we had asked the sponsor to justify the results of an embryo-fetal development study in rabbits, in which fewer external or visceral findings than would ordinarily be expected were noted (the study was done in a lab known to produce fewer findings than studies done in other labs). The sponsor asserted that the incidence of these findings in this study was consistent with the historical rate in similar studies performed by this lab. Because this did not adequately address our concerns (in some sense it confirmed the problem), Drs. Roney and Freed request that the sponsor repeat the study in Phase 4; I agree.

Review of the high dose rat carcinogenicity data reveals the occurrence of a single melanoma in 130 animals (0.77%). This is a rare finding in an albino rat, although background rates of about 0.1% to over 0.5% have been reported in the literature (the higher estimates of the background rate were obtained in studies of a different strain of albino rat than was used in this study). Further, a single tumor ultimately diagnosed as a neurofibrosarcoma in a control female was given a differential diagnosis that included melanoma, with the note that ultrastructural examination would be necessary to make the diagnosis definitively. As far as we know, this was not done, and it is not clear how the final diagnosis was arrived at.

Finally, it is worth noting the previously identified statistically significant increase in combined lung adenoma/adenocarcinoma in the mouse (the low effect dose had an AUC of about 170 times that at the human dose, with an AUC at the NOEL of only about 5 compared to that at the human dose), and the three positive chromosomal aberration assays.

CMC

Numerous CMC requests were made, all of which appear to have been adequately addressed.

Clinical Pharmacology and Biopharmaceutics

We had asked the sponsor to formally evaluate the effects (if any) of levodopa on rasagiline clearance (the original data were contradictory), and to adopt specific dissolution specifications.

The sponsor did not evaluate the effects of levodopa on rasagiline clearance; they accepted our draft labeling, which described the contradictory results. However, we did not expect that language to stand; we had anticipated that it would be revised upon a definitive resolution of the question. I believe that this should be done, but can be done in Phase 4.

The sponsor has adopted our proposed dissolution specifications.

Finally, there has been some question about the adequacy of the characterization of the kinetics of rasagiline, especially at the 1 mg dose, and especially in patients with renal or hepatic impairment.

We have discussed this issue in depth with Drs. Baweja and Jackson of OCPB. We agree that the sponsor has provided adequate (although not ideal) data on the kinetics of a 1 mg dose in healthy subjects. There is an approximate 50% increase in AUC from Day 1 to Day 7. There is an approximate doubling of AUC at steady state in patients with mild hepatic or mild renal disease compared to normals. There is an approximate 7 fold increase in the AUC at steady state in patients with moderate liver disease compared to normals, and we have no reliable data on the levels of rasagiline at steady state in patients with moderate-severe renal disease (the doubling of AUC in patients with mild renal disease compared to normals is somewhat difficult to explain, given that renal excretion makes a very small contribution to rasagiline's elimination. However, given this observed doubling of AUC, it is impossible to predict plasma levels at increasing degrees of renal dysfunction). Further, clearance decreases about 1% for each year of increasing age.

There is some evidence that the kinetics may be non-linear at doses greater than 1 mg. Specifically, the AUC at steady state at a 2 mg dose is about 4 fold that seen at steady state at a 1 mg dose. However, this is based on cross-study comparisons (the sponsor did not evaluate the kinetics of a 1 and 2 mg dose in the same study), and can only be considered a preliminary conclusion at this time. Dr. Jackson has recommended that the sponsor evaluate the kinetics of 1 mg and higher doses in a single study.

Although dosage adjustments are possible in patients with mild renal or hepatic disease, it is impossible, given current dosage strengths, to appropriately adjust the dose in patients with moderate-severe hepatic disease, and the absence of information about the effects of moderate-severe renal disease argues, in my view, for the sponsor to perform an adequate study in these patients.

COMMENTS

The sponsor has responded to the requests included in the Approvable letter. Those requests related to issues other than the melanoma and tyramine issues have generally been adequately addressed, although I believe that several issues still do need to be further addressed (if the drug is approved, these can be completed in Phase 4).

With regard to the melanoma question, the sponsor has responded to our request for dose response analyses. A trend for a dose response was seen; although the results are difficult to interpret, especially given the different conditions of the studies from which these results were derived (for example, active screening was instituted at very different times in the course of the PRESTO and TEMPO studies), I believe the finding is of some interest. In particular, it bears noting that it is probably the case that a greater proportion of the exposure at the 2 mg dose (in which the greatest tumor rate was noted) was under conditions of decreased tumor surveillance than that for the lower doses (recall that the 2 mg experience was primarily obtained in TEMPO and its follow-on open label extension, which was much further along than PRESTO when active screening was instituted). This suggests that the increased tumor rate seen in the 2 mg dose group may actually be artifactually low compared to the rates in the lower dose groups.

The sponsor has further responded to our request to further analyze the data from Study EP002. We have focused on this study because it was done in North America, and included a population of patients most comparable to those enrolled in the AAD prospective screening study. Overall, the observed/expected ratio was about 5 in the PD patients compared to that seen in the AAD population, although, as described earlier, there are factors that make this ratio somewhat uncertain; as Dr. Jones notes, a marked (17-fold) increase in the O/E ratio was seen for in situ tumors, with a 1.2 O/E ratio for invasive tumors. Dr. Jones finds this discrepancy possible evidence that other factors (besides PD and/or its treatments) may be influencing melanoma appearance in this cohort. In her view, this discrepancy, then, raises questions about the interpretation of the data.

Of course, it is impossible to rule out such other factors (for example, as discussed earlier, she postulates one explanation for this observation; there may, of course, be many others). I would add that, for the reasons previously mentioned (secular trends in melanoma occurrence, inclusion of Canadian data in EP002, and the lack of complete medical records for suspicious tumors in the AAD study), there is reason to believe that the overall finding may not be an entirely accurate estimate of the contribution of PD as an independent risk factor for melanoma.

However, these data are at least consistent with the conclusion that patients with PD (and being treated for it) have an increased rate of melanoma occurrence compared to age and sex matched controls (a previously cited study in the literature also suggests that PD is associated with about a two fold increased risk of melanoma compared to the general population). In the light of this observation, the previous analyses that demonstrated a 2.5 relative risk for melanoma in the NDA database compared to that seen in the AAD data (and the less compelling comparisons to the SEER database, which also demonstrated an increased O/E ratio compared to background) must, in my view, be questioned as providing strong evidence that rasagiline is tumorigenic. Of course, this increased relative risk may well be a reflection of rasagiline's tumorigenic potential, but the EP002 data now make such a conclusion somewhat less obvious.

However, other data and analyses also suggest that rasagiline use may be associated with an increased risk of the occurrence of melanoma compared to patients with PD not receiving treatment with rasagiline. Most, but not all, of these analyses and data were available at the time of the Approvable action.

To summarize, a comparison of the rate of melanoma (invasive and in situ) in the NDA database that includes only the first 6 tumors detected (prior to the institution of active screening) with rates in other NDA databases reveals a rate of 5.8 tumors/1000 PYs, compared to the next highest rate of 1.6 tumors/1000 PYs in the pramipexole NDA.

Further, comparison of the Immediate and Delayed Start portions of the TEMPO and PRESTO studies provide potentially useful data on this question.

As described earlier, these studies should be capable of providing meaningful analyses of tumor formation over time. Theoretically, if there is a latency to tumor occurrence (and detection), patients in the Immediate start groups should have more tumors than those in the Delayed start groups, and this difference should be most prominent at the later time points, given that at any point in calendar time (corresponding to a particular data cut-off date), patients in the Immediate start groups had more exposure to drug. As was seen, however, the pattern of tumor detection in these studies was quite different. In PRESTO, most of the tumors (again, the numbers are small in any case) were seen in the first 6 months in the Immediate start group, with decreasing numbers over time. In contrast, in TEMPO, most of the tumors were seen in the Immediate group at the latest time epoch (>24 months). As Dr. Jones points out, this discrepancy in distributions of time to diagnosis may have been confounded by the timing of the institution of active screening (which was instituted very late in the conduct of TEMPO, and much earlier in the conduct of PRESTO). However, within each study, the timing of the onset of active screening was controlled for, as, of course, was the duration of PD (itself, as we have seen, a possible risk factor for

melanoma). Whether it is appropriate, given the discrepant results, to “pool” the results, as we had asked the sponsor to do, is open to question.

It is difficult to interpret these different patterns of tumor diagnoses over time in the two studies. If we expect extended exposure to be associated with an increase in tumors, the results of TEMPO, where the bulk of tumors were seen out late in time (again, the numbers are relatively small) are particularly disturbing, but the results of PRESTO are not consistent with this explanation. Given the view that increased exposure should be associated with increased tumor rates, I cannot explain the PRESTO findings. The finding could simply be a reflection of the variability of the data, as could the finding of late occurring tumors in TEMPO (although, again, the latter finding, taken by itself, is consistent with a meaningful finding, and, in my view, not ignorable).

It is also true, as previously described, that the “hazard” for melanoma does not follow a monotonically increasing pattern with time, as we might expect (refer to the description of the rates for various time intervals earlier in this review and in Dr. Jones’s review), given the relatively similar rates at the 0-.5, .5-1, and >3 year epochs, although there does appear to be a hint of an increasing risk over time between the 1-2, 2-3, and >3 year epochs. This, too, is an observation that is difficult to explain, although scenarios can be constructed to explain it to be consistent with the expected increase in hazard over time. However, looking at the data pooled in this way is complicated by many factors, including the different times in each included study that active screening was instituted.

Finally, rasagiline is considered carcinogenic in the mouse (increased incidence of lung tumors) and genotoxic (clastogenic). I believe the finding of a single melanoma in the high dose rat is entirely uninterpretable (given a finite background rate, and the possible occurrence of a melanoma in a control animal).

These data, taken together, raise important questions about rasagiline’s capacity to cause melanoma in people. Previously, we had decided that this issue could be handled with appropriate labeling and a commitment by the sponsor to further evaluate this in a controlled trial in Phase 4. However, upon further reflection, I believe, along with the review team, that the evidence at this time is sufficiently suggestive of rasagiline’s capacity to cause melanoma (primarily, the increased incidence of melanoma in the NDA database compared to those seen in other NDAs for PD treatments, the late occurring tumors in the TEMPO study, and the possible signal for a dose response for tumor occurrence; the animal findings contribute somewhat, though minimally, to my thinking) that a more definitive answer to this question should be obtained prior to approval. As numerous members of the team point out, at this time there is no evidence that rasagiline provides any additional benefit above that provided by currently available treatments for PD.

Could we approve it at this time with appropriate labeling? Although a case can be made for doing so (I made such a case previously, in support of the previous Approvable action, when most, although not all, of the analyses we have at this time were available), I believe the signal for melanoma is sufficiently unclear that it will be important to definitively decide (to the extent possible) whether or not rasagiline causes melanoma before we can decide if it should be marketed. It should be pointed out that, even with very close monitoring, tumors did occur during clinical development, and, of course, would be expected to occur if the drug were to be approved (in any event, the sponsor does not believe that frequent monitoring is necessary, or that our proposed Phase 4 study needs to be performed). Although it is impossible to quantitate the risk for melanoma were the drug to be approved, it seems to me, at this time, given all of the data, that the risk (if any) should be better defined prior to approving the drug.

It is of interest that, of all the drugs for which we have requested data on melanoma, we have not received this information for selegiline, the one drug that is most similar to rasagiline in its mechanism of action. One could argue that, given the similarities between these two drugs, and the absence of tumor data for selegiline, the presumption is that selegiline is likely to have the same capacity for tumor formation as rasagiline, and that, therefore, it would not be inappropriate to approve rasagiline at this time. I disagree. Regardless of the fact that the question of selegiline's capacity to cause melanomas is unaddressed at this time, we believe that there is a signal for rasagiline; it is, of course, possible that, despite the similarity in the drugs, they could have different risks for melanoma (of course, we do not have a detailed understanding of the mechanism of melanoma formation, assuming that the signal is real). In any event, we believe that there is a signal for rasagiline, and therefore this needs to be further investigated / —

Regarding the question of rasagiline's capacity to induce a hypertensive crisis in the face of an unrestricted diet, as Dr. Kapcala points out, the sponsor has not provided any new substantive evidence to refute our previous findings.

It should be pointed out that there is no real signal in either the formal tyramine studies or the home blood pressure monitoring done in PRESTO, or in the entire safety database itself, suggestive of such an effect (although the analyses of the home BP monitoring requested by Dr. Kapcala might be considered to provide very slight evidence of increased BP with rasagiline; even here, though, the "effects" are quite small and inconsistent).

However, as Dr. Kapcala finds, none of our previous concerns have been adequately addressed. Importantly, our concerns that the Paris study was

inadequate because so few subjects responded to the high dose of 800 mg have not been addressed at all. The sponsor cites several articles that describe eliminating subjects from formal tyramine studies if they do not respond to high tyramine doses, but they provide no quantitative data on the number of such subjects who do not respond to tyramine doses of 800 mg or higher. Again, our experience with data from other NDAs has been that all subjects respond to doses lower than 800 mg. Therefore, we are left with our original concern that the Paris study is unreliable, and, in addition, because the sponsor used the same tyramine product in its other challenge studies, this concern carries over to the interpretation of these studies as well.

Further, as we had previously noted, we have additional concerns about these other studies because the tyramine was administered with a meal in all three. As Dr. Kapcala reiterates, the literature suggests that tyramine given with a meal results in markedly lower peak levels and a much more prolonged exposure than when given in the fasted state. We have essentially no information about whether or not tyramine given *with* a meal (in capsule form) results in the same profile of absorption as the same amount of tyramine given *in* a meal (that is, a meal consisting of tyramine-containing foods). As we had previously noted, we questioned whether the sponsor's decreased frequency of BP monitoring in the three other challenge studies was adequate to detect any possible hypertensive reactions, and those questions still exist. Further, we do know that at least one article in the literature documents that, with a drug known to have a tyramine sensitivity factor of 5 (which is certainly likely not the case with rasagiline), the peak BP effects of a meal to which tyramine was added were almost all (83%) seen at 150 minutes or later, and in the PRESTO home BP monitoring, about 95% of the measurements were made before this time point. In summary, then, both in the three challenge studies, as well as in the PRESTO home BP setting, we still have serious questions about whether or not the BP assessments were adequate (in terms of time after meals) to detect hypertensive reactions if they occurred.

A clear unknown is what degree of tyramine sensitivity, as assessed in a formal, fasting tyramine challenge study, correlates with the likelihood of a hypertensive reaction after a high tyramine-content meal. Knowledge of this relationship would be very helpful in deciding whether a drug with a given degree of tyramine sensitivity (as assessed in a formal study) actually poses a risk to patients in a real-world setting. As Dr. Kapcala notes, a "typical" high tyramine meal probably contains no more than 50 mg of tyramine. However, how this relates to the sorts of doses used in standard tyramine challenge studies is unknown. More to the point, however, we have no confidence that the studies done by the sponsor to address these questions have done so adequately (in addition to the question of the timing of BP measurements, it should be recalled that in the three challenge studies, doses of tyramine of up to 75 mg were administered, but the tyramine product was the same as that used in the Paris study, the results of which raised questions about the bioavailability of this product). So, we have little confidence

that in the challenge studies the patients were actually exposed to sufficient tyramine, in the challenge studies and the PRESTO home BP monitoring study we have no confidence that the BP measurements were appropriately timed to dosing, and in the PRESTO home BP study, we have no information about the tyramine content of the meals. For these reasons, (as well as the observation that there may be a signal for a "cheese" reaction at the 2 mg dose, and, given various factors [e.g., concomitant 1A2 inhibitors, potential non-linear kinetics at doses above 1 mg], some patients receiving 1 mg may achieve levels close to those typically achieved in patients receiving 2 mg; of course, if there is a true signal at 2 mg, what levels of rasagiline between those typically achieved at 1 and 2 mg are associated with the cheese reaction are unknown) I would agree with Drs. Kapcala and Feeney that the potential for rasagiline to induce a hypertensive reaction in the face of an unrestricted diet has not been adequately characterized, and should be prior to approval, unless the sponsor would be willing to adopt labeling that calls for a restricted diet (at the moment, of course, they do not believe that this is necessary).

I realize, of course, that the interpretation of either of these issues (melanoma, tyramine reactions) is not straightforward, and others could reasonably conclude that both issues could safely be further characterized after approval.

Specifically, the data speaking to the potential increased risk for melanoma are complicated, and not entirely consistent or explainable under the presumption that increased duration of exposure to rasagiline should result in increased rates of tumor formation. Additionally, although lung tumors were seen in the mouse, these are a common tumor type, and the in vitro chromosomal aberration studies that were positive are typically the most sensitive genotoxicity assays performed. Nonetheless, for the reasons described above, I do believe that the data, taken as a whole, should be considered to at least raise significant questions about rasagiline's capacity to cause melanomas, and, also for the reasons given above, I believe that these questions should be more definitively addressed prior to its marketing.

In addition, there is no real signal that rasagiline causes hypertensive reactions in the absence of dietary tyramine restrictions. This is true whether we examine the data in formal challenge studies, in the PRESTO home BP monitoring study, or in the database as a whole. Despite the deficiencies cited, there are no well-documented cases of tyramine-related hypertensive reactions in the database. However, as I have tried to argue, I believe the deficiencies in the data are such that, in spite of the lack of such documented cases, rasagiline's capacity to cause such reactions in the setting of an unrestricted diet need to be better characterized before it is approved.

For these reasons, we recommend that the sponsor be sent another Approvable letter, with a requirement for a well-designed study to evaluate the risk for melanoma, as well as for a definitive tyramine challenge study.

Finally, as I have described above, there are other issues that need to be addressed, but these can be done in Phase 4 (definitive blood pressure study, rhabdomyolysis reporting requirements, repeat embryo-fetal development study in rabbits, further evaluation of the effects of levodopa on rasagiline clearance, additional study in patients with moderate-severe renal disease, evaluation of the kinetics of 1 mg and higher doses in one study). If the NDA is not approved at this time, some of these studies can be done prior to approval, depending upon the timing of the sponsor's response to the Approvable letter.

Russell Katz, M.D.

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/s/

Russell Katz
8/4/05 04:15:23 PM
MEDICAL OFFICER

MEMORANDUM

NDA 21-641 Agilect (Rasagiline Mesylate)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Response to Approvable Letter

DATE: July 22, 2005

Background

On July 2, 2004, the sponsor was sent an Approvable Letter for Agilect (at doses of 0.5-1 mg/day) for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunctive therapy with levodopa. While the review team believed the sponsor had established the effectiveness of Agilect, the review team did not believe that the sponsor had adequately assessed the risks of 1) tyramine reactions and 2) melanoma with Agilect.

Tyramine

Rasagiline is a selective MAO-B inhibitor with a structure similar to selegiline. It has the potential to lose selectivity for MAO-B at higher exposures. The sponsor had performed 4 tyramine challenge studies with Agilect and, additionally, had collected a large quantity of home blood pressure monitoring data in patients taking Agilect without a tyramine-restricted diet. The data from these studies showed that rasagiline has the potential to lose selectivity at a dose of 2mg/day, with a few patients having fairly significant blood pressure elevations after a tyramine challenge.

If the tyramine-challenge data is viewed separately for patients on Agilect monotherapy and patients taking concomitant levodopa, there was a relative lack of data for patients taking concomitant levodopa at doses of Agilect greater than 1mg/day (only n=6, with 2 of the 6 having BP elevations). In one formal tyramine-challenge study of patients taking concomitant levodopa, several patients taking Agilect 0.5mg/day had significant blood pressure elevations, but a placebo patient in the same study also had a comparable effect. The home-BP monitoring showed no significant BP effects, but again this was all at a dose of Agilect 1mg/day. For patients taking Agilect monotherapy, there were 2 formal tyramine-challenge studies (with n=25 subjects treated with 2 mg/day), but no home-BP monitoring. The data at the 2mg/day dose of Agilect, as monotherapy revealed a few patients having significant blood pressure elevations.

Rasagiline is metabolized primarily by CYP1A2 and inhibitors of 1A2 have the ability to almost double the exposure to rasagiline. Therefore, if 1mg/day were viewed as selective for MAO-B and 2 mg/day as non-selective, then concomitant use of Agilect 1

mg/day with a drug that was a 1A2 inhibitor would result in non-selectivity for MAO-B. Therefore, the Approvable labeling noted that Agilect should not be used concomitantly with 1A2 inhibitors without a tyramine-restricted diet.

Methodological problems with all 4 of the formal tyramine-challenge studies were raised in the Approvable Letter. In the usual tyramine-challenge study, tyramine is provided in a fasting state. In 3 of the 4 studies, the tyramine was given in close proximity to food, potentially reducing exposure as well as the Tmax of exposure. At the least, this variation from the usual tyramine study made comparisons to previous tyramine studies with other drugs almost impossible. Also, while it might seem ecologically valid to provide a tyramine challenge with food, there are no direct comparisons available of encapsulated tyramine with food to a standard tyramine-rich meal. And finally, if the Tmax is prolonged but BP monitoring is not comparably extended, peak effects on BP could be missed.

For all the reasons above, the Approvable Letter asked the sponsor to conduct an adequate tyramine sensitivity study, incorporating a number of important elements that were outlined in the letter. If the sponsor chose not to perform such a study, the Approvable Letter offered the option of Approved Labeling restricting use to patients on tyramine-restricted diets.

Melanoma

During the development of Agilect, 16 melanomas were identified with a rate of 8 cases per 1000 person-years. After the sixth case was identified, active surveillance for melanoma was instituted in clinical trials. Both the rate of melanoma pre-screening and the rate of melanoma post-screening exceed rates from comparable epidemiologic databases (SEER of the NCI without screening and the American Academy of Dermatology Skin Cancer Screening Program). The sponsor had argued that the excess risk was no greater than that seen in other Parkinson's disease populations.

Because of DNDP's concerns about the signal, in the Approvable labeling, the Warning section recommended monitoring for melanoma on a frequent and regular basis, ideally by a dermatologist. The Approvable Letter also asked that the sponsor conduct a large simple trial post-approval to compare melanoma rates to patients exposed and unexposed to rasagiline.

In the Approvable Letter, the sponsor was asked to:

- 1) Provide dose-response information on melanoma.
- 2) Provide data from a cohort of North American Parkinson's disease patients that the sponsor had already studied. Patients were actively screened for melanoma in that study and DNDP wanted to perform an analysis of the risk of melanoma from this actively-screened PD population compared to the actively-screened American Academy of Dermatology Skin Cancer Screening Program.

3) Perform a pooled analysis of all cases of melanoma observed in clinical trials (during screened and unscreened periods combined and including controlled and open-label time), comparing the numbers of melanomas for patients a) randomized to Agilect from the start to b) patients with a "delayed start" of Agilect.

Of additional note, rasagiline was found to be mutagenic and clastogenic and was associated with an increased incidence of lung adenomas/carcinomas in the mouse carcinogenicity study. One high-dose animal in the rat carcinogenicity study developed a melanoma, apparently an extremely rare tumor in albino rats.

Other Issues

There were miscellaneous other issues raised in the Approvable Letter.

1. ECGs from the TEMPO study should be centrally re-read and then analyzed. The need for a formal QT study would be re-assessed after examining those results.
2. Further analyses of "flu syndrome" should be conducted.
3. Further analyses of lab and vital sign data should be conducted.
4. The sponsor should clarify the reason for discontinuation for the 7% of patients that discontinued without attribution to a specific AE.
5. Miscellaneous chemistry issues needed to be addressed.
6. For the carcinogenicity study in rats, microscopic analysis of tissues in the low and mid-dose groups was requested because the high-dose group exceeded a maximally tolerated dose, based on weight loss.
7. The sponsor was asked to formally evaluate the effect of levodopa on rasagiline clearance.

Tyramine Sensitivity

The sponsor has not performed a new tyramine-challenge study. The sponsor believes the previous studies establish the safety of Agilect at a dose of 1 mg/day. Dr. Kapcala has reviewed the sponsor's arguments. He continues to believe that a new study is needed.

Potency of Tyramine in the Paris Study

The potency of the tyramine used in this study was brought into question because a fair number of subjects did not have a BP response even to doses of 800mg of tyramine.

The sponsor responded to this concern by stating that subjects are frequently preselected for such studies, based on tyramine requirements in these higher ranges. Dr. Kapcala reviewed a group of about 100 randomly selected patients and found that all responded to tyramine at doses less than 800mg. Therefore, this issue has not been fully addressed.

Home BP Monitoring in PRESTO Study

While the sponsor refers to roughly 40,000 home BP measurements in this study, Dr. Kapcala notes that only about 10,000 measurements were analyzed. Many of the measurements were excluded for pre-specified reasons, to include recording of unrealistic values, leaving the smaller subset.

Dr. Kapcala also notes that the exclusion of measurements more than a few hours after meals may have systematically eliminated values of interest, since BP elevations in cheese reactions can occur late.

Dr. Kapcala also notes that all of the home BP data were collected at a dose no greater than 1 mg/day. Thus, there is limited data on a dose of 2 mg/day with concomitant levodopa from home BP recording. Given that exposures after 1 mg/day may, under certain circumstances, approach exposures after 2 mg/day, and given that there may be a PD interaction between levodopa and MAO inhibitors, it would seem important to document more experience at 2 mg/day with levodopa.

Reduced Bioavailability of Tyramine From Capsules Consumed With Food

Dr. Kapcala has pointed to published references in which significant reductions in bioavailability of tyramine when taken in capsule form with food are reported. The sponsor has no data to refute this finding. Therefore, the tyramine challenges in 3 of the 4 formal tyramine-challenge studies may have been inadequate.

Melanoma

Dr. Lisa Jones has reviewed the safety data from this submission, to include the new melanoma data.

Dose-Response Analysis

The dose-response analysis performed at our request proved to be ambiguous because of the small numbers of cases and the limited exposure at each dose studied.

North American Screening Comparison

The sponsor did provide data from their own North American study in which patients with Parkinson's disease were actively screened for melanoma. Dr. Jones performed an

age- and sex-matched comparison of this data to data she had previously obtained from the American Academy of Dermatology screening program. To my knowledge, this is the first comparison, incorporating active screening, of a Parkinson's disease population to the background population. Overall the observed/expected ratio was 5.3 (95% CI: 3.1-7.9). The overall result was driven primarily by an observed/expected ratio of 16.7 for melanoma in situ. The observed/expected ratio for invasive melanoma was 1.2.

Earlier in 2005, Olsen et al (Br J Cancer. 2005 Jan 17;92(1):201-5) published the results of a review of the Danish Cancer Registry from 1977-1998 (results previously submitted by the sponsor as part of the NDA). Among the 14,000 patients with Parkinson's disease, the standardized incidence ratio for malignant melanoma was 1.95 (95% CI, 1.4-2.6).

The observed/expected ratio of 5.3 in Dr.Jones' analysis at least suggests that the Olsen finding is not artifactual. Active screening for melanoma would be expected to improve the sensitivity for finding an increased risk and, indeed, the Dr.Jones' comparison suggested a higher risk than the Olsen study. I believe the increased risk for melanoma in situ in Dr.Jones' analysis (16.7) should increase the level of concern. Active screening might be expected to eliminate some of the lead-time detection bias during which in situ cases would progress to invasive melanomas.

Unanswered by either of the above studies is whether the increased risk (now fairly established by these 2 studies) is due to Parkinson's disease or the drugs used in the treatment of PD.

Additional information about the sponsor's PD cohort and the AAD cohort would strengthen the findings. Specifically, more information about the relative north-south representation in the 2 cohorts would be useful. Also, more information should be presented about the numbers of biopsies performed in the 2 cohorts and the ratios of positive biopsies/total biopsies for the 2 cohorts.

"Delayed-Start" Comparison

The controlled trials performed with Agilect would generally be viewed as too short to provide a meaningful comparison for melanoma risk (6 month, placebo-controlled). However, if after the controlled portion of the trials all patients were switched to active drug and followed forward, a comparison can be made between patients who were initially started on active drug and patients who had start of active drug delayed for 6 months. That is the case in the Agilect development program.

Such a comparison has been done for the North American trials, PRESTO and TEMPO, individually and combined. The data was accrued through February 2004. There were 17 melanomas altogether. For the 2 studies combined, among the roughly 300 patients with a delayed-start of Agilect, there were 2 melanomas. Among the roughly 600 patients with an immediate start of Agilect, there were 15 melanomas.

For PRESTO alone, among the roughly 150 patients with a delayed start of Agilect, there was 1 melanoma. For the roughly 300 patients with an immediate start, there were 6 melanomas.

For TEMPO alone, among the roughly 150 patients with a delayed start of Agilect, there was 1 melanoma. For the roughly 300 patients with an immediate start, there were 9 melanomas.

These results of the delayed-start analyses, reproduced in both PRESTO and TEMPO, suggest an increased risk of melanoma with Agilect.

In theory, the delayed-start analysis is intended to show that the longer the exposure to Agilect, the greater the risk of melanoma. Ideally, then, the incidences of melanoma for the delayed-start group for sequential time epochs should mirror those of the immediate-start group, once the lead-time is eliminated. This is not the case for PRESTO. And for TEMPO, the between-group difference is driven by late-occurring melanomas in the immediate-start group and there is no comparable on-drug follow-up for the delayed-start group.

Melanoma Discussion

During the original NDA review, DNDP compared the American Academy of Dermatology screening program results to the melanoma data from a subgroup of all rasagiline patients (those in North America who were actively screened and for whom risk factor data was available, roughly 600 patients). The results from that comparison are reproduced below:

Invasive Melanoma				In Situ Melanoma			
Observed	Expected	Obs/Exp	95% CI	Observed	Expected	Obs/Exp	95% CI
4	1.5	2.6	0.7-6.7	6	0.6	10.2	3.7-22

The observed/expected ratios above seem to mirror those from the new comparison of the background PD population to the AAD population. If, for the AAD/Agilect comparisons, invasive melanoma and in situ melanoma are considered together, the number observed is 10 while the expected is 2.1, with an observed/expected Ratio of 4.7 (95% CI: 2.3-8.7). For the AAD/background PD population comparisons, the overall observed/expected ratio is 5.3 (95% CI: 3.1-7.9).

In my review of the original NDA data, I had thought it unlikely that the high observed/expected ratios observed for melanoma overall and especially for melanoma in situ could be explained by an increased risk in Parkinson's disease alone. Dr. Jones' new analysis seems to highlight a definite increased risk of melanoma in Parkinson's patients, an increased risk that may be considerably higher than previously described. Her results certainly merit public dissemination.

At the same time, the results of the delayed start analysis suggest that rasagiline increases the risk of melanoma. While, the pattern of melanoma incidence over time in the delayed-start group of PRESTO does not mirror that of the immediate-start group, it may be unreasonable to expect such a perfect pattern in support of an increased risk with increasing exposure, given the small numbers of cases. Rather I chose to be impressed by the replication (in PRESTO and TEMPO) of the overall between group difference that shows an excess of melanomas in the immediate-start groups, thereby implicating Agilect.

The safety team is recommending that a large simple trial be performed *pre-approval* to address the risk of melanoma with Agilect. I concur. In the Approvable letter, such a study was requested *post-approval*.

Biopharm Review

Dr. Andre Jackson has reviewed the biopharm data in this submission. During interactions with the sponsor during the review cycle, it became clear to Dr. Jackson that much of the PK data previously submitted by the sponsor was faulty in that AUCs were computed with inadequate numbers of datapoints. In some cases, AUCs were computed from only 2 datapoints. This problem was especially true for the 1 mg/day data.

The AUCs at 1 mg/day appear small and not dose-proportional to the AUCs reported for 2 mg/day. Whether this non-linearity is real or an artifact of the AUC computation is unclear at this time.

For this reason, the biopharm group recommends:

1. A dose-proportionality study at 1 mg/day, 2 mg/day, and 6 mg/day.
2. It is also recommended that the sponsor attempt to improve the assay sensitivity.

Overall Conclusions

Dr. Lisa Jones' new analysis of the AAD/EP002 comparison suggests that, in comparably screened North American populations, the risk of melanoma in Parkinson's disease patients (not on Agilect) is higher than might be expected from previous studies in non-screened patients. This result seems to merit public dissemination as it bears on the frequency of melanoma screening in all patients with Parkinson's disease.

At the same time, the results of the delayed-start analyses of TEMPO and PRESTO suggest that Agilect increases the risk of melanoma in patients with Parkinson's disease. This needs further consideration.

Dr. Kapcala has reviewed the sponsor's responses to our methodological concerns about the 4 tyramine challenge studies conducted with Agilect. There continues to be a concern that the tyramine in the Paris study had lost its potency. There continues to be a concern that the administration of tyramine in the other 3 studies in close proximity to food diminished the bioavailability of the tyramine compared to the more standard tyramine challenge studies done in the fasting state.

There is evidence to suggest that rasagiline at a dose of 2mg/day (especially with concomitant levodopa) may no longer be selective for MAO-B; this could lead to possible clinical sequelae. Also, there is very limited experience presented for patients taking concomitant levodopa and a dose of 2 mg/day of Agilect. Of the 6 such patients in formal tyramine challenge studies, 2 had significant elevations in BP.

At the same time, the PK of rasagiline at a dose of 1mg/day has not been adequately characterized. Without adequate characterization of the PK at 1mg, we do not know how close we are at 1 mg/day to exposures that might be non-selective. If the PK is non-linear between 1 mg/day and 2 mg/day, then even small variations might push exposures markedly out of the "selective" range of exposures.

Therefore, a further tyramine challenge study is recommended to better characterize the selectivity of rasagiline at different doses. Because of the possibility of a PD interaction between rasagiline and levodopa, I would also like to see this combination studied at a dose of 2 mg/day Agilect. Absent additional tyramine studies, the sponsor's proposal is

Without knowing the time course of the return of MAO-A activity after dose reduction, DNDP's approach of instituting a tyramine-restricted diet in such patients seems more reasonable.

Recommendations

Another Approvable Letter should be sent requesting that the sponsor further address the above concerns about tyramine sensitivity and the risk of melanoma.

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/s/

John Feeney
7/22/05 12:27:33 PM
MEDICAL OFFICER

**CLINICAL REVIEW : Response to Approvable Letter
(Rasagiline-Related Tyramine Sensitivity)**

Application Type	NDA
Submission Number	21641
Submission Code	AZ
Letter Date	11/04/04
Stamp Date	11/04/04
PDUFA Goal Date	8/4/05 (with 3 month extension)
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	6/30/05
Established Name	rasagiline
(Proposed) Trade Name	Agilect
Therapeutic Class	dopaminergic agonist
Applicant	TEVA Neurosciences
Priority Designation	S
Formulation	tablet
Dosing Regimen	Once Daily
Indication	Monotherapy of Early Parkinson's Disease and Adjunctive Therapy of Advanced Parkinson's Disease
Intended Population	Early and Advanced Parkinson's Disease

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1. EXECUTIVE SUMMARY

Background

This NDA (originally submitted 9/9/03) for treatment of early (monotherapy) and advanced (adjunctive therapy Parkinson's Disease) was reviewed and the Agency issued (7/2/04) an approvable letter describing several concerns. The most significant concerns revolved around the Agency's concern : 1) that the risk of increased tyramine sensitivity (i.e. the selectivity of MAO inhibition for MAO-B vs MAO-A) to rasagiline had not been adequately characterized at various doses, including 1 mg and 2 mg daily; and 2) for the risk of developing melanoma or acceleration of growth of melanoma that was already present. The Agency had recommended that the sponsor conduct a new study to characterize the risk of increased sensitivity to tyramine. The Approvable letter further noted that if the sponsor did not want to conduct the recommended tyramine study, then the product labeling would need to require that patients restrict the diet with regard to tyramine containing products.

The sponsor met with the DNDP on 9/27/04 to discuss Agency concerns identified in the Approvable letter and submitted an electronic Response to the Approvable letter on 11/4/04. The sponsor's response assesses the sponsor's response solely on the concern about increased sensitivity to tyramine associated with rasagiline treatment. It is pertinent to note that I was the original clinical reviewer who assessed the efficacy and tyramine sensitivity of rasagiline (Clinical Review entered 6/29/04 and signed 7/1/04).

Overview of the Sponsor's Response

The sponsor's response to Agency concerns about rasagiline increasing tyramine sensitivity consists of 3 parts : Part 1) opinions of the sponsor's expert consultant (Drs. Ira Shoulson) regarding pharmacodynamic actions of rasagiline on tyramine sensitivity, Part 2) the sponsor's overview of all data in the rasagiline development program; and 3) the sponsor's response to specific questions/comments made by the Agency in the Approvable letter. **There were no new data nor significant new data analyses submitted in the response that were not available in the original NDA submission. The totality of the 3 part response regarding rasagiline effects on tyramine sensitivity consisted of : 1) a reiteration or somewhat modified presentation of similar points and arguments articulated in the original submission; and 2) a point by point address of Agency concerns about inadequacies of characterizing the effect of rasagiline on tyramine sensitivity that had been outlined in the Approvable letter.**

In this review, I have summarized arguments and/or data provided by the sponsor in regard to Agency concerns about increased tyramine sensitivity associated with rasagiline treatment. In some instances, I have provided direct quotes from the sponsor's response. Following the various sections of the sponsor's response, I have provided my comments on the sponsor's response.

The following introductory comments, Executive Summary and Main Points Why Dietary Tyramine Restrictions Are Unnecessary have been abstracted from Part 2 of the Sponsor's response and essentially summarize the most important points and response arguments also contained in Parts 1 and 3 of the response. The introductory comments, Executive Summary, and Main Points are shown in italics as a direct quotes of the sponsor. These quotations serve as the sponsor's summary arguments against the need for dietary tyramine restriction with rasagiline treatment at ≤ 1 mg daily. **At the end of this presentation, I have provided my main comments related to the sponsor's response.**

Much of the review of rasagiline and tyramine sensitivity relates to the concept of Tyramine Sensitivity Factor (TSF). The TSF is calculated by dividing the control/pre-treatment tyramine threshold dose (dose required to increase systolic blood pressure by a certain amount such as ≥ 300 mg Kg) by the post-treatment tyramine threshold dose for each subject and is synonymous with the term tyramine pressor ratio (TPR).

Sponsor's Introductory Comments

"In the approvable letter of Agilect dated 2 July 2004, the FDA expressed its concern that the selectivity of rasagiline 1 mg/day for MAO-B has not been adequately demonstrated in the 4 tyramine challenge studies provided in the NDA. We would like to address the Division's concerns about the selectivity of rasagiline 1 mg/day for MAO-B in our answers below by providing additional insight and clarifications and emphasizing few aspects that were included in the submission (see Appendix 1), but the Sponsor felt they deserved additional attention. The goal of this response document is to address the Agency's concern that the selectivity of rasagiline 1 mg/day for MAO-B has been demonstrated during the clinical program and to convince the Agency that rasagiline could be approved without tyramine dietary restrictions."

SPONSOR'S EXECUTIVE SUMMARY

"The aim of this overview document is to emphasize why the data demonstrates that restrictions of dietary tyramine are unnecessary in patients treated with rasagiline at the clinical doses (0.5 mg/day and 1 mg/day) and that patients can administer rasagiline with a sufficient safety margin. The Sponsor assessed the potential for a pharmacodynamic interaction between rasagiline mesylate and tyramine in healthy volunteers and Parkinson's Disease (PD) patients who participated in four different controlled clinical trials as part of the development program for rasagiline mesylate :

- 1. In healthy volunteers treated with rasagiline only (without levodopa, rasagiline doses of 1 mg and 2 mg in comparison to selegiline 10 mg)*
- 2. In PD patients treated with levodopa and rasagiline (1 mg and 2 mg)*
- 3. In PD patients on long term rasagiline monotherapy (1 mg and 2 mg)*
- 4. In PD patients on levodopa and long term rasagiline (0.5 mg and 1 mg)*

1. The tyramine challenge in healthy volunteers (Study P94159) was the first clinical pharmacology study in the rasagiline clinical program to assess the potential tyramine

pressor effect before we had any human data for the selectivity of rasagiline for MAO B inhibition. For this reason, the study was conducted in healthy volunteers. The decision to perform the challenge under fasting conditions was made to allow for the most extreme conditions in order to be able to assess the true potential for a tyramine reaction in the most sensitive way. Twenty seven healthy volunteers administered escalating doses of tyramine (50 mg . 800 mg) under fasting conditions. The endpoint was defined as the dose of tyramine which induced an increase in systolic blood pressure of 30 mmHg or more compared to the baseline systolic blood pressure (before administration of tyramine) (TYR30). The sensitivity to tyramine (TSF) was defined as the ratio between TYR 30 while on placebo treatment and the TYR 30 after repeated dose rasagiline treatment. A group of subjects dosed with once daily 10 mg/day selegiline was included as comparison because selegiline at this dose is in clinical use for long time without tyramine restrictions. The results showed that once daily 1 mg rasagiline did not increase the sensitivity for tyramine compared to placebo. A slight increase in sensitivity to tyramine was observed, compared to placebo, for subjects receiving 2 mg rasagiline and 10 mg selegiline. The results obtained with selegiline in this study are compatible with those reported in the literature (Elsworth 1978)1 and therefore, validate this study. Although this study was conducted in young healthy volunteers, its results are also valid for older population. Pharmacokinetic data from phase I studies in young healthy volunteers were pooled and were compared with pooled data from phase I and II studies conducted in healthy subjects as well as PD patients, representing an older subject population. It has been shown that regardless of differences in subjects characteristics, older subjects had similar exposure parameters to those of younger healthy subjects. Moreover, results from population PK studies conducted in PRESTO and TEMPO (samples taken up to 3 hours after dosing) indicate that rasagiline levels at 1 mg and 2 mg doses are comparable to those observed in young healthy volunteers.

Therefore data in young subjects in the tyramine study is also valid for older subjects. The same is true for gender.

2. Pharmacodynamic interactions study between rasagiline and tyramine in PD patients on levodopa/carbidopa (Study TVP-1012/132). Nineteen PD patients on rasagiline and chronic levodopa/carbidopa received sequential doses of 25, 50 and 75 mg tyramine before breakfast starting on Day 23. The endpoint was defined as a clinically significant increase in systolic or diastolic blood pressure (BP) following tyramine administration. Two patients treated with 2 mg rasagiline (on 50 mg and 75 mg tyramine, respectively) had transient, short-term, self limited elevations in BP that did not necessitate pharmacological intervention. These were considered a probable tyramine-rasagiline interaction, although for one patient (#209) this determination is questionable (he did not respond to tyramine challenges of 25,50 and 75 mg and had only elevation in BP after the second 75 mg challenge). The other patient (#206) showed marked blood pressure variations during the course of the study, even in the absence of rasagiline. In both cases, the BP elevations were asymptomatic and were not accompanied by significant changes in heart rate or ECG recordings. None of the patients receiving 1 mg rasagiline showed any suspected tyramine-rasagiline interaction or even an elevation in BP.

3. Tyramine tolerance sub-study in the pivotal monotherapy study (TEMPO, TVP-1012/232). *In the tyramine sub-study performed on the last day of the 6-month double-blind, placebo-controlled phase, fifty five (55) patients were challenged with 75 mg tyramine 30 minutes after a light meal. The endpoint was defined as an increase in systolic BP of more than 30 mmHg or a decrease in heart rate to 40 bpm or less for 3 consecutive measurements. None of the challenged patients reached the pre defined endpoint for a tyramine-MAO inhibitor interaction as stated in the protocol. For two patients, both on 2 mg rasagiline, the Data Safety Monitoring Committee had looked into moderate increases in systolic blood pressure, although the BP changes were not consistent with the pre-defined criteria for a tyramine-MAO inhibitor interaction and the absolute values were not consistent with a classical tyramine MAOI reaction. There were no blood pressure elevations in the 1 mg rasagiline group or in the placebo group.*

4. A tyramine challenge sub-study was also performed as part of the pivotal adjunct therapy study (PRESTO, TVP 1012/133). *The design of this study was similar to that of the TEMPO study, with a rasagiline/placebo ratio of 2/1. Patients were challenged on the last day of the double-blind placebo-controlled phase after being treated for 6 months with rasagiline. Fifty five (55) patients were challenged with 50 mg tyramine after completing a light meal. The end points were identical to those in the monotherapy study. Four patients (3 on rasagiline 0.5 mg, one on placebo) had systolic blood pressure increases that met the end point, 3 consecutive measurements of more than 30 mmHg increase from baseline. Additional 2 patients (both on placebo) had blood pressure elevations that did not meet the end point (similar increases but in 2 consecutive measurements only). A blinded review of all BP curves, prior to code opening, by a CVS expert resulted in an identification of 6 patients as having signal of BP increases - 3 were on rasagiline and 3 on placebo.*

In addition to this tyramine challenge sub-study all the patients in PRESTO (N=472) underwent an intensive BP monitoring to detect any potential BP increase that might be related to tyramine in meals. Home blood pressure measurements, pre and post prandial (45 and 90 min after the main meal of the day), were taken by the patients for 7 days at baseline, after 3 and 26 weeks of treatment. A total of approximately 41,000 measures were reviewed by the independent safety committee (DSMC). It was concluded by the committee that there was no increase in the incidence of BP elevations in rasagiline treated patients. Statistical analysis of the data demonstrated that events of blood pressure increases (including the severe ones) were equally distributed between treatment groups.

In several European countries, people usually consume foodstuff containing higher amounts of tyramine than in the US. Notwithstanding, the average amount of tyramine in a typical and abundant meal including alcoholic beverages, rarely rises above 30-40 mg. It is unlikely, therefore, that a five-course 50 mg tyramine meal would be frequent. Even if so, a large quantity of cheese would be required to provide a sufficient dose of tyramine to have the pressor response. It should be realized that this quantity of cheese would also provide a large amount of lipid that reduces the absorption and therefore the bioavailability of tyramine leading to a reduced risk of blood pressure elevation. In contrast, the same amount of tyramine administered in capsules under fasting condition results in increased

bioavailability of tyramine and therefore expected to cause an increase in BP.

Based on the data presented, the following may be concluded regarding rasagiline treated subjects challenged with high and non-physiological doses of tyramine :

In healthy volunteers receiving rasagiline 1 mg daily there was no increase in sensitivity to tyramine at doses up to 800 mg in comparison to placebo.

Although in the clinical pharmacology study (rasagiline adjunct to levodopa/carbidopa, Study 132) there was a suspected tyramine/rasagiline response in one patient and the second patient was questionable, both on 2 mg rasagiline and high tyramine doses, it should be noted that these patients received tyramine after an overnight fast prior to the consumption of morning meal resulting in an increased absorption compared with fed conditions. Moreover, it is known that tyramine in capsules under fasting conditions has a more pronounced effect than the same tyramine content originating from food. In addition, although in the tyramine challenge sub-study of the monotherapy trial (Study 232) there was a modest elevation of blood pressure in two patients on 2 mg rasagiline (in response to amount of tyramine much higher than can be obtained in a high tyramine containing meal), none of the patients on the 1 mg rasagiline in both the above-mentioned studies showed any alterations in blood pressure in response to this challenge. In a trial with rasagiline (0.5 mg, 1 mg, and placebo, Study 133) as adjunct to levodopa/carbidopa therapy, several cases of transient asymptomatic blood pressure elevations were observed in response to the tyramine challenge, however these were observed in both rasagiline and placebo patients, thus not indicating any increased sensitivity to tyramine that might be attributed to rasagiline effect.

A comparison of rasagiline and selegiline based on published papers (Elsworth 1978 and Schulz 1989)^{1,2} and on experimental data in one study with rasagiline and selegiline in healthy volunteers suggests that 2 mg rasagiline is comparable to 10 mg selegiline with regard to the potential for tyramine interaction. Selegiline at doses up to 10 mg/day has been in use for many years both as monotherapy and as adjunct to levodopa therapy without any dietary restrictions.

In the PRESTO Study (133), a total of 472 patients underwent intensive BP monitoring under real life conditions in order to identify any potential BP elevation that might be related to tyramine in the meal. No such relationship could be identified from the results of all treatment groups.

Therefore, it is concluded from these results that 1 mg rasagiline with or without levodopa could be administered safely without dietary tyramine restrictions.”

“MAIN POINTS WHY DIETARY TYRAMINE RESTRICTIONS ARE UNNECESSARY

1. Due to rasagiline selectivity for the inhibition of MAO-B compared to MAO-A, only a significant inhibition of MAO-B is achieved at the recommended clinical dose (1 mg/day).

Tyramine challenge studies following 6 months of rasagiline treatment showed that the selectivity is maintained with a long-term treatment.

2. Rasagiline at clinical dose of 1 mg/d is more selective than selegiline at the clinical dose of 10 mg/d and selegiline is administered with no dietary restrictions.

3. With the clinical dose of 1 mg/d there was never any indication of increased sensitivity to tyramine (healthy subjects and PD patients with and without concomitant LD treatment).

4. There is no indication for increased sensitivity to tyramine based on the level of DHPG, the pharmacological marker for MAO-A activity in humans. It is evident that rasagiline at clinical recommended dose (1 mg) and even at a dose two times higher than the recommended dose (2 mg) is fully selective for MAO-B.

5. Home blood pressure (BP) measurements (approximately 41,000 individual measurements in 472 PD patients on chronic LD therapy) prior to and following meals demonstrated even distribution of sporadic BP elevation episodes between rasagiline (1 and 2 mg) and placebo groups, namely no BP increases that could be attributed to rasagiline and tyramine in food in real life setting.

6. All patients in pivotal studies and most patients in the entire clinical program did not restrict their diet of tyramine and the cardiovascular (CVS) adverse event profile was comparable to placebo/entacapone.

7. No increase in frequency of CVS serious AEs (CVA, MI, TIA) was observed in rasagiline treated patients.

8. The asymptomatic pressor response seen in one clinical pharmacology study with twice the clinical dose (Study 132) was obtained under extreme conditions that could not be achieved in the real life situation.

9. Rasagiline at the clinical dose can be administered with no tyramine restrictions with or without LD with sufficient safety margin."

Sponsor's Conclusion :

- Dietary tyramine restriction is not necessary for ≤ 1 mg daily rasagiline treatment of Parkinson's Disease patients who do not have significant factors (mild or worse hepatic insufficiency or concomitant treatment with CYP1A2 inhibitors) increasing rasagiline exposure.

Reviewer Comments

Overview

My assessment of this response has not changed my view that another critical tyramine challenge study (under fasting conditions) still needs to be conducted prior to approval in order to characterize the tyramine sensitivity of rasagiline treatment adequately. This response did not contain any new data nor analyses that allowed me to change my conclusion that remains the same as outlined in the Approvable letter. This response is mainly a reiteration of numerous points and arguments that were contained in the original NDA and that were not sufficiently compelling to convince me that this drug could be approved without dietary tyramine restriction. The sponsor's arguments were not adequately convincing in the original NDA submission and the repeat articulation of these same arguments, occasionally with a different twist or emphasis, remain unconvincing.

I have also summarized my main comments here about specific issues/considerations that are relevant to rasagiline-related tyramine sensitivity and that had been argued/articulated in this response.

Tyramine Bioavailability in Food and Tyramine Challenge Studies With Food and Blood Pressure Responses

The sponsor still has not adequately addressed my concerns that subjects challenged with tyramine (25 – 75 mg) added to food and ingested just prior to or just after eating in 3 studies received a significant challenge with tyramine and that the monitoring was sufficient to have captured a threshold pressor response. Based upon the published literature, it is clear that there is a marked decrease in bioavailability of tyramine when it is added to food and that the pharmacokinetics of tyramine (e.g. particularly T_{max} and shape of the plasma tyramine curve) is markedly altered. More specifically, ingesting tyramine added to food results in a marked delay in T_{max}, the plasma tyramine “peak” becomes flattened, and the pressor response is attenuated. My detailed comments and concerns are outlined within the review.

In summary, it is not clear that the lack of a tyramine pressor threshold response represents a true negative. A tyramine challenge confounded by adding tyramine to food and presenting this challenge near a meal requires validation that the tyramine challenge is sufficient for assessing a threshold pressor response. However, the sponsor had adopted this investigational approach without providing any validation that this experimental approach is satisfactory for assessing drug-induced tyramine sensitivity. Of significant relevance to the sponsor's approach, one important publication showed that a range of 150 mg to 500 mg (mean 306 mg) of tyramine added to food was required to produce a tyramine systolic blood pressure response of ≥ 30 mm Hg when administered with a drug that produced a 5 fold increase in tyramine sensitivity. Given this study result, and the assumption that perhaps rasagiline did not enhance tyramine sensitivity beyond a 5 fold increase, one would not seem to expect a significant tyramine pressor response to 25-75 mg tyramine added to food and administered near a meal as was done in the sponsor's studies.

Fasting Tyramine Challenge Study

The sponsor has not adequately addressed my concerns about the limitations and shortcomings associated with the sponsor's fasting tyramine study (P94159) that were outlined in the Approvable Letter. I consider that this study as providing only preliminary data on rasagiline-induced tyramine sensitivity. I believe that a fasting tyramine challenge study is the main way to characterize drug-induced tyramine sensitivity. This has been the main way from a regulatory perspective. Once fasting tyramine responses have been characterized at a range of different drug (e.g. rasagiline) doses, then the significance of changes in drug-induced tyramine sensitivity can be assessed relative to the risk for provoking a hypertensive "cheese" reaction. Considering the numerous limitations, shortcomings, and concerns with the sponsor's sole fasting tyramine challenge study, I believe that a different perspective about tyramine sensitivity risk (i.e. increased tyramine sensitivity and pressor risk at daily rasagiline ≥ 1 mg) could result from completing a more comprehensive fasting tyramine challenge study according to previous DNDP recommendations outlined in the Approvable Letter.

Home Blood Pressure Monitoring

The sponsor re-presented home blood pressure monitoring data derived from the PRESTO study. **However, it is important to recognize that this study assessed only 0.5 and 1 mg rasagiline daily and not 1 and 2 mg daily as erroneously noted in the sponsor's Main Points summary.**

The sponsor noted that its analyses of home blood pressure monitoring did not suggest a concern regarding hypertensive effects of rasagiline related to eating. In presenting these data regarding home blood pressure monitoring, the sponsor did not clearly indicate nor emphasize that it had analyzed a much smaller body of data (particularly post-treatment post-meal measurements) to arrive at its conclusions. In particular, Table 3 in Part I of the sponsor's response seemed to suggest that the frequency of threshold pressor responses was based upon nearly 41,000 total measurements in 3 treatment group but a closer analysis revealed that these threshold pressure responses reflected a much smaller body of data (~ 16,500 readings). Although approximately 65,000 blood pressure readings had been collected in the PRESTO study at baseline and post-treatment at pre- and post-meal times, approximately 25,000 (nearly 40 %) were excluded from primary safety analyses assessing threshold pressor increments related to eating at home for a variety of reasons (most of which had been pre-specified in an analysis plan). Of the approximately 40,000 remaining readings, approximately 16,500 were post-meal measurements collected at various times after eating but mainly relatively "early" (e.g. within 150 minutes after eating).

Approximately 95 % of the usable post-meal blood pressure measurements (~ 16,500 total within 3 treatment groups) occurred **within 150 minutes** of the meal. Considering that a relevant publication showed that peak pressor responses occurred **after 150 minutes** after ingesting tyramine added to a meal in the vast majority of subjects (83 %), it seems possible that the sponsor's study design of focusing on "early" post-meal blood pressure readings could have missed significant delayed pressor responses after eating. Consequently, I have a major concern

that the sponsor's study design may not have been sufficiently sensitive to capture rasagiline meal-related pressor response, presumably related to tyramine contained within the meal. Furthermore, it could have been more reassuring if there were data showing that 2 mg daily rasagiline treatment was not associated with an increased frequency of moderate or severe pressor response after eating. However, the sponsor did not collect data in the study assessing the efficacy of 2 mg rasagiline.

I would also note that some additional analyses that I requested raised a suspicion of hypertensive responses after eating and associated with rasagiline treatment for particular hypertensive outlier data. The sponsor submitted analyses of outlier hypertensive responses at baseline, during treatment, and the **treatment difference incidence (i.e. change from baseline) of outliers**. These analyses show a greater treatment difference incidence (12.2 %) of a moderate post-meal systolic blood pressure increment (> 30 mm Hg to > 140) for the 0.5 mg rasagiline group compared to the 1 mg rasagiline (5.3 %) and placebo (7.7 %) for groups. In contrast, the treatment difference for the more "severe" post-meal systolic blood pressure increment (> 30 mm Hg to > 180) for the low dose rasagiline was slightly greater (2.0 %) than that of placebo (1.4 %) and the higher dose rasagiline was even greater (3.0 %) than those for both groups, suggesting some dose-dependence. These analyses indicate a **treatment effect (rasagiline % – placebo %)** of + 0.6 % for 0.5 mg rasagiline and + 1.6 % for 1 mg rasagiline for this more severe hypertensive outlier response. Thus, these analyses might be suggestive of a rasagiline-related dose-dependent increased incidence of more severe meal related systolic blood pressure increments in particular at risk patients.

I also asked the sponsor to submit analyses of for hypertensive outlier rate (**# outliers/total # measurements**) data at baseline, during treatment, and the **treatment difference (change from baseline = treatment rate – baseline rate) for the outlier rate**. The treatment difference of outlier event rate for moderate systolic moderate post-meal systolic blood pressure increment (> 30 mm Hg to \geq 140) was similar in all 3 groups. However, the treatment difference was considerably higher for 0.5 mg rasagiline (+ 0.0017) and 1 mg rasagiline (+ 0.0006) compared to placebo (- 0.0002) for the more "severe" post-meal systolic blood pressure increment (> 30 mm Hg to > 180). These analyses indicate a **treatment effect (rasagiline rate – placebo rate)** of + 0.0019 for 0.5 mg rasagiline and + 0.0008 for 1 mg rasagiline. Although these increased treatment effects for the more severe increment are not dose-dependent, it is interesting to recall that the sponsor's tyramine challenge data associated with food and near a meal from this same study (PRESTO) had shown increased tyramine-induced systolic blood pressure increments in the 0.5 mg rasagiline group.

Hypertensive "Cheese" Reactions and Cardiovascular Adverse Events

There were no apparent hypertensive crises (i.e. tyramine induced "cheese reactions") in the safety experience to date at daily rasagiline doses of \leq 2 mg. My original review had noted one case of subject receiving 10 mg daily who seemed to have a hypertensive "cheese reaction" crisis. The overall number of Parkinson's Disease exposed to any dose of rasagiline is 1361 as per the most recent Safety Update in this submission. Furthermore, the number of patients exposed to 2 mg daily is relative low (110) and relatively few patients (19) have received higher

doses (4 or 10 mg daily). Thus, 1342 patients were exposed to daily doses of ≤ 2 mg daily. Using the "rule of 3" for assessing the maximal risk of a rare event, it would seem that the risk for a hypertensive "cheese reaction" at doses of < 2 mg daily is 3/1342 (0.2 %), and possibly much lower.

Based upon the most recent Safety Update, 62 % (1466 patient-years/2363 patient-years of the rasagiline exposure was under conditions in which there was no dietary tyramine restriction. Thus, 38 % or 897 patient-years of exposure occurred with dietary tyramine restriction. Although most patients (95 % - 1288/1361) had been treated with rasagiline either as monotherapy or adjunctive therapy without dietary tyramine restriction at some time, the duration of treatment in these patients varied so that the exposure was much longer without tyramine restriction for some patients compared to others. Considering even if rasagiline treatment was associated with a risk for a "cheese reaction," this risk ought to be markedly diminished during dietary tyramine restriction. Thus, if one assessed the maximal risk of patients who had been treated without tyramine restriction for any duration, "the rule of 3" would give a similar maximally limited risk (0.2 % - 3/1288) as calculated irrespective of tyramine restriction. These calculations only emphasize the possibility that the risk of tyramine-induced hypertensive "cheese reactions" could still occur with a significant, unacceptable frequency if rasagiline exposure without dietary tyramine restriction was permitted in a large population. Thus, the absence of detecting any "cheese reactions" in this extremely limited exposure experience is not necessarily that reassuring.

Question of Increased Exposure Related to Female Gender, Age and Concomitant LD Treatment, Inadequacies of Pharmacokinetic Data for Rasagiline, and Pharmacokinetic Concerns Related to Tyramine Sensitivity

- There are various suggestions of increased rasagiline exposure (e.g. ranging from 30 % to 70 % or more) in females vs males but the quality of these data are not good. Thus, the question remains unanswered whether female exposure is greater than males and if so, how much? The sponsor has suggested that there is no effect of gender. However, a closer analysis of PK data revealed serious deficiencies/inadequacies with regard to PK sampling. In many PK studies of healthy subjects and studies of Parkinson's Disease patients at 0.5 and 1 mg rasagiline daily, typically there are only 3 measurable plasma rasagiline levels and the initial sample is the highest level. The accuracy of AUC calculations is not likely to be reliable and it is not clear that the C_{max} proposed (the first sampling time, usually 0.5 hours) is necessarily the true C_{max}, that could occur earlier. Comparison of AUC across studies at 1 mg rasagiline daily shows that small number of healthy females subjects shower marked differences (up to 3 fold) and a similar phenomenon in males (up to 2 fold difference). The sponsor did not critically review and discuss these data.

This discovery of the inadequacies of some of the PK data collection has raised serious doubt about the adequacy of the PK program relative to an approval. As a minimum requirement, the Biopharmaceutical reviewer (see Dr. Andre Jackson review) thinks that the sponsor should conduct : _____ a dose proportionality

study prior to approval. Accurate data about the effect of hepatic impairment on rasagiline exposure is a very critical issue because rasagiline is metabolized by liver and the previous data (that are not considered clearly reliable), suggested nearly a doubling of exposure in the face of mild hepatic impairment and a several fold increased exposure in the face of more severe impairment.

Population PK data suggest an increase of rasagiline exposure (AUC) of ~ 1 % per year. There are minimal PK data collected in elderly subjects (≥ 65 years) and no PK study assessed rasagiline in healthy elderly vs non- elderly subjects within the same study to determine whether there are differences. Thus, the question of increased rasagiline exposure in elderly patients also remains unanswered.

Finally, one population PK study suggested increased rasagiline exposure with concomitant LD therapy but another did not. Although the sponsor conducted a drug-drug interaction PK study assessing the effect of rasagiline on LD, unfortunately, the sponsor in that same study did not assess the effect of LD on rasagiline. Thus, the possibility exists that concomitant LD treatment could also increase rasagiline exposure.

The suggestion of increased exposure in females may not necessarily be that dramatic (e.g. several fold difference) in isolation. However, I suggest that a modest mean increase of 30-50 % could be worthy of consideration given the possibility that this difference could be associated with other factors (age, concomitant LD, hepatic impairment, concomitant treatment with metabolic inhibitor of CYP1A2) increasing exposure. The net additive effect of these several factors could potentially result in a several fold increased exposure (compared to subjects without these factors increasing exposure) for a certain dose such as 1 mg daily. For example, a subject with these combined factors resulting in a cumulative 300 % increased exposure might experience an AUC similar to an AUC of subjects treated with 4 mg. Given the facts that : 1) we already have a suspicion that there is increased tyramine sensitivity to 2 mg daily rasagiline; 2) the extent of this increased tyramine sensitivity is not precisely quantified; and 3) we have no idea of the extent of the risk of increased tyramine sensitivity for a normal healthy subject treated with 3 or 4 mg daily, this unsettled issue is an important one that should be resolved prior to approval of rasagiline.

These PK issues have a potentially important impact on the tyramine sensitivity issue because increased rasagiline exposure would be expected to be associated with increased tyramine sensitivity. We already have questions about how well tyramine sensitivity (during rasagiline treatment) is characterized in the uncomplicated state of young, healthy males. The possibility that many of these factors could appreciably increase rasagiline exposure (and thereby tyramine sensitivity) emphasizes the importance of characterizing tyramine sensitivity related to rasagiline treatment more comprehensively across a wider rasagiline dose range and determining the potential impact of various factors on rasagiline PK (i.e. exposure) prior to approval.

Additional Considerations

- The sponsor has not directly addressed a significant concern related to the tyramine challenge program such as my concern about the potency of the tyramine in Paris study (P94159) and tyramine used in other studies in which it was added to food and administered near meals. This concern is based upon the observation that in the sponsor's fasting study (P94159), a very large percentage (67 % - 18/27) of subjects required a very high tyramine threshold dose (800 mg) or did not exhibit a tyramine pressor threshold response (TYR30) at doses up to 800 mg. This experience is a marked outlier from my review of the literature and FDA data (105 baseline/pre-treatment tyramine challenge tests in 84 subjects exhibited a TYR30 threshold at ≤ 700 mg tyramine).
- In considering the risk/benefit assessment of rasagiline, rasagiline does not seem to present a clear, major scientific advance over treatment already used in U. S. for early and advanced Parkinson's Disease. Although selegiline (selective MAO-B inhibitor) has been approved for adjunctive treatment of Parkinson's Disease in U.S. for many years, it is also used in the U.S. and worldwide "off-label" as monotherapy for early Parkinson's Disease. Thus, when considering rasagiline-related risk (e.g. especially concerns about tyramine sensitivity not adequately characterized and concern for possible melanoma) vs its benefit (in the face of many medical therapies available for adjunctive and monotherapy treatment of Parkinson's Disease in the U.S.), I think that a clear benefit of rasagiline should be evident to justify the risk of an approval. At this time, I do not consider an approval of rasagiline justified relative to the present safety risks.
- A 2004 publication based upon the results of the TEMPO study describes an effect suggestive of neuroprotection by rasagiline (but only 2 mg daily dose) in early Parkinson's Disease. I am concerned that if rasagiline is approved at 0.5 and 1 mg daily doses, 2 mg would be used off-label to delay disease progression. Already, many review articles, refer to this study and that its results are suggestive of neuroprotection. Given that there is a concern about the risk of tyramine-related hypertensive "cheese" reactions with 2 mg daily rasagiline treatment (there is no question that 2 mg is associated with increased tyramine sensitivity, only the quantitative increased risk remains unclear), especially in conjunction with other factors (age, gender, LD, hepatic impairment) that may increase rasagiline exposure by unknown amounts, rasagiline-related tyramine sensitivity should be characterized more comprehensively and at higher dose exposures that could be produced by factors increasing rasagiline exposure. These considerations are particularly important given the fact that the TEMPO study is only suggestive of disease progression delay effect and results from this study would not suffice as a pivotal study showing delay of disease progression for a variety of reasons outlined in my original review.

Reviewer's Overall Perspective / Assessment

- **Overall, the sponsor's response on the tyramine sensitivity issue is mainly a recapitulation of previous arguments articulated in the original submission. This response did not include any new substantive data nor new analyses that had not been available previously. In many instances, the sponsor has reviewed data or publications in a somewhat superficial manner and did not seem to provide a very critical, objective assessment of data and issues of concern. It is the sponsor's responsibility to show that rasagiline is safe and especially with respect to risk of tyramine sensitivity and hypertensive "cheese" reactions. When the assessment of the safety of rasagiline related to tyramine sensitivity is largely indeterminate because of limitations in the extent and quality of data collected, the burden should not rest with the Agency to guess and hope that rasagiline is safe relative to tyramine sensitivity. It is not appropriate nor prudent for the Agency to approve the drug and let the tyramine sensitivity issue be resolved post-approval as a result of the post-marketing safety experience. My overall assessment is that the sponsor has not adequately demonstrated the safety of rasagiline relative to tyramine sensitivity and needs to do this prior to approval.**

Reviewer Conclusions :

1. **The available data have not adequately characterized the effect of rasagiline on tyramine sensitivity and thus the risk for serious hypertensive "cheese reactions" cannot be adequately assessed relative to when tyramine restriction is necessary and when tyramine restriction is unnecessary.**
2. **There are 3 other significant considerations (1. rasagiline does not represent major advance as medical option for Parkinson's Disease; 2. unresolved, serious concern about risk of melanoma with rasagiline; 3. serious risk that a higher rasagiline 2 mg daily dose will be used because of a publication suggesting possible delay of Parkinson's Disease and this dose is associated with increased risk for hypertensive tyramine-related "cheese" reaction) that support my recommendation for an approvable action at this time. I view these considerations as supportive of my recommendation and would still recommend the same approvable action at this time even if these 3 considerations did not exist.**
3. **The sponsor must conduct the tyramine challenge study (under fasting conditions) previously recommended by the Agency prior to approval and adequately characterize the risk for increased tyramine sensitivity.**

Recommended Action :

I recommend an approvable action at this time relative to the need to collect additional data to characterize the risk of tyramine sensitivity to rasagiline treatment.

Recommendations

Requirements Prior to Approval

1. Conduct a randomized, double-blinded, placebo-controlled study (under fasting conditions) to characterize the risk more precisely and comprehensively for rasagiline-induced tyramine sensitivity. Such a study should be designed to address concerns, problems, limitations and shortcomings of Study P94159. Such considerations include :
 - 1) studying larger numbers of older (30 – 60 years old), healthy subjects ($N \geq 20$ per treatment group) including males and females
 - 2) comparing multiple treatment groups including 1, 2, 4, 6 mg rasagiline daily, placebo, selegiline 10 mg daily mg BID), and positive control group (non-selective MAO inhibitor)
 - 3) requiring 3 consecutive systolic blood pressure increments ≥ 30 mm Hg to define tyramine threshold dose relative to mean of 3 pre-tyramine systolic blood pressures after blood pressure monitoring at 5 minute intervals over 3 hours
 - 4) administering multiple tyramine challenge doses for pre-treatment (50, 100, 200, 300, 400, 500, 600, 700, 800 mg) and post-treatment (12.5, 25, 50, 100, 200, 300, 400, 500, 600, 700, 800 mg) administered on separate consecutive days
 - 5) ensuring that the tyramine used for challenges has adequate biological potency
2. Conduct a dose proportionality PK after multidosing (e.g. 0.5, 1, 2, 4, 10 mg) of rasagiline at steady state. This study could also be designed to answer age and gender questions by nesting appropriate stratification of subjects by age (elderly ≥ 65 years old vs younger/non-elderly < 40 years old) and gender.
3. Conduct a renal — PK study after multidosing (1 mg) of rasagiline because results of the previously conducted renal — studies are not deemed reliable and these are important factors that could increase rasagiline exposure.

Other Recommendations (Not Required for Approval)

1. Conduct a formal PK study comparing the PK parameters of 1 mg rasagiline daily treatment (steady state) with respect to age (elderly ≥ 65 years old vs younger < 40 years old) and gender.
1. Conduct a formal PK study assessing the effect of LD on rasagiline PK parameters / exposure.

2. INTRODUCTION AND BACKGROUND

2.1. Parkinson's Disease and Current Therapies

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of melanin-containing neurons in the substantia nigra pars compacta resulting in a reduction in the striatal dopamine. The disease is clinically manifested by bradykinesia, tremor, rigidity and postural instability. The disease develops in adulthood with the peak onset at 55-60 years. The prevalence rate is approximately 300 per 100,000 and about 60,000 new cases are diagnosed annually. The cause of PD is, at the present time, unknown.

Presently, pharmacological intervention in PD is symptomatic. Augmentation of impaired dopaminergic neurotransmission is the backbone of therapy. Treatment of PD includes anticholinergic drugs to reduce the relative excess of striatal cholinergic activity accompanying dopamine deficiency; MAO-B inhibitors to inhibit the breakdown of dopamine in the Central Nerve System (CNS); dopamine agonists to supplement neurotransmission at the dopamine receptor level; and amantidine, which has shown a modest effect on PD symptoms. Symptomatic relief is often transient, as neuronal loss continues or tolerance develops.

The current standard treatment is primarily based on a dopamine replacement strategy using the dopamine precursor LD. LD is converted by dopamine decarboxylase in residual nigrostriatal neurons to dopamine, and temporarily restores the depleted dopamine stores in PD patients. The combination of LD with carbidopa (a peripheral decarboxylase inhibitor) leads to a preferential elevation of the level of dopamine in the brain. LD dramatically reduces morbidity and mortality in PD. However, long term treatment is associated with involuntary movements (dyskinesia), neuropsychiatric side effects and debilitating fluctuations in motor response following a dose of LD, which are known as .ON. (good mobility) and .OFF. (impaired mobility) periods. After five years of LD treatment, about 50% of PD patients are not adequately controlled. Therefore, some specialists believe it is desirable to delay the onset of LD treatment in patients with early PD as long as possible.

Inhibition of MAO-B, the major enzyme metabolizing dopamine in the human brain, may help conserve the depleted supply of dopamine and delay the need for exogenous LD. Selegiline (deprenyl) is a site-directed, irreversible ("suicide") inhibitor of MAO-B. In a large scale clinical study, selegiline was shown to significantly delay the time to LD in patients with early PD. Other studies have demonstrated the beneficial effect of selegiline and another MAO-B inhibitor, lazabemide, in PD patients.

A proposed mechanism through which MAO-B inhibition confers neuroprotection is by preventing the conversion of dopamine to hydrogen peroxide and the activation of other potential neurotoxins. Recent experiments have shown that selegiline appears to have anti-apoptotic effects. However, adverse effects, including activation of pre-existing gastric ulcers

and occasional hypertensive episodes, may accompany treatment with selegiline. Furthermore, L-selegiline is metabolized to L-methamphetamine and L-amphetamine, which may cause undesirable side effects such as anxiety, tachycardia and insomnia. Therefore, a MAO-B inhibitor without amphetamine metabolites could be useful in the treatment of Parkinson's Disease, both as monotherapy and as an adjunct to LD treatment. It is relevant to note that no drugs are approved in the U.S. for delaying disease progression of Parkinson's Disease.

Rasagiline (N-propargyl-R-aminoindan) is an irreversible MAO inhibitor with high selectivity towards the B form of the enzyme. It is distinctive from selegiline in several aspects. The major metabolite of rasagiline in humans, 1-R-aminoindan (AI), is devoid of amphetamine-like properties and is not likely to interfere with cardiovascular function, or to exert neurotoxic effects. On the other hand, beneficial effects of AI on restoring hypoactivity and preventing cognitive impairment were demonstrated in several experimental animal models.¹⁸ Rasagiline is five times more potent than selegiline in antagonizing MPTP-induced neurotoxicity and protects neurons from injury in a variety of experimental models, both in-vitro and in-vivo. Even without concomitant use of LD, rasagiline restores normal behavior and locomotion in experimental models of dopamine hypofunction.

2.2. Brief Summary of Major Highlights of Regulatory History of IND 45958 for Rasagiline

- IND filed: August 5, 1994
- End of Phase II Meeting: June 18, 1997
- Meeting with FDA regarding tyramine and study TVP-1012/132: December 16, 1999
- Meeting with FDA regarding tyramine and study TVP-1012/232: March 10, 2000
- Meeting with FDA regarding tyramine and future study TVP-1012/133(PRESTO): August 17 & 23, 2000
- Meeting with FDA regarding melanoma in the development program: April 6, 2001
- Meeting with FDA regarding melanoma in the development program: August 20, 2001
- Pre-NDA meeting: April 30, 2003
- NDA submitted: September 5, 2003
- 120 day safety update submitted: December 23, 2003

This NDA was reviewed and the Agency issued an approvable letter describing several concerns. The most significant concerns revolved around the Agency's concern: 1) that the risk of increased tyramine sensitivity (i.e. the selectivity of MAO inhibition for MAO-B vs MAO-A) to rasagiline had not been adequately characterized at various doses, including 1 mg and 2 mg daily; and 2) for the risk of developing melanoma or acceleration of growth of melanoma that was already present. The Agency had recommended that the sponsor conduct a new study to characterize the risk of increased sensitivity to tyramine. The Approvable letter further noted that if the sponsor did not want to conduct the recommended tyramine study, then the product labeling would need to require that patients restrict the diet with regard to tyramine containing products.

The sponsor (including its consultants Dr. _____ and Ira Shoulson) met with the DNDP on 9/27/04 to discuss the Agency's concerns about increased sensitivity to tyramine and melanoma. The sponsor argued that it did not think that there were concerns for a risk of tyramine hypertensive reaction at 1 mg daily rasagiline. The DNDP informed the sponsor that it was welcome to make whatever arguments it wanted to convince the Agency that another tyramine study was not necessary prior to approval nor that dietary tyramine restriction was needed in the absence of the sponsor conducting the recommended tyramine study prior to approval. In that meeting this reviewer specifically "noted that, in his personal view, the sponsor's data and package containing the sponsor's various arguments against safety concerns for tyramine reactions (with rasagiline treatment) did not suggest anything new that changed his view about the need for the tyramine challenge study recommended by the DNDP."

On 11/4/04 the sponsor submitted an electronic Response to the Approvable letter. This review will review the sponsor's response solely on the concern about increased sensitivity to tyramine associated with rasagiline treatment.

I refer the reader also to my Clinical Review (entered 6/29/04; signed 7/1/04) of the original submission of this NDA. This review includes extensive discussion of my concerns about the adequacy of the data characterizing the sensitivity to tyramine (and potential for hypertensive "cheese" reactions) associated with rasagiline treatment.

For convenience of the reader, I have provided the Executive Summary of tyramine sensitivity issue related to rasagiline from my original review.

2.3. Reviewer's Executive Summary of Tyramine Sensitivity Issues for Rasagiline from Reviewer's original NDA review

Summary of Tyramine / Pharmacodynamic Study Results

Study P94159 Tyramine Challenge in Healthy Young Males

This double-blind placebo-controlled study assessed tyramine sensitivity (regarding blood pressure) pre- and post-treatment in young, healthy males during dietary tyramine restriction. Three groups (group 1 – rasagiline 1 mg QD; group 2 – rasagiline 2 mg QD; group 3 – selegiline 10 mg QD) of subjects were studied sequentially and randomized to placebo (n = 3) or active drug (n = 6). Beginning on day 8 of treatment, subjects were administered increasing doses of tyramine (in capsule, 50 – 800 mg) once or twice daily and blood pressure was monitored for a protocol-defined tyramine threshold pressor response (≥ 30 mm Hg systolic blood pressure above pre-tyramine value; TYR30). Subjects were also studied with increasing tyramine doses before treatment. Tyramine sensitivity factor (TSF) was determined by comparing tyramine threshold doses in Period 1 (pre-treatment) / Period 2 (post-treatment).

Main Results

The table below shows TSFs only for subjects who demonstrated a protocol defined pressor response of tyramine in both periods. In 18 out of 29 subjects, 800 mg tyramine was required to show a threshold pressor response or there was no such response at any dose up to 800 mg.

Table 1 Mean TSF Ratio Based Upon Actually Meeting Protocol Specified Criterion (≥ 30 mm Hg SBP Increment)

Protocol P94159	Tyramine Sensitivity Factor (Period1/Period2) (Per Protocol)				
	Mean	Std	N	Min	Max
Treatment Group					
DEPRENYL (Selegiline) 10mg QD	4.33	3.51	3	1.00	8.00
PLACEBO	1.10	0.55	5	0.50	2.00
TVP-1012 1mg QD	1.25	0.50	4	1.00	2.00
TVP-1012 2mg QD	2.80	1.10	5	2.00	4.00

Plasma tyramine levels of subjects treated with each dose of rasagiline and selegiline typically showed increased (relative to placebo) ratios of Period 2/ Period 1 plasma tyramine suggesting some inhibition of MAO-A after treatment. In most instances there was a suggestion of dose-dependence because the 2 mg group ratio was usually higher than that for the 1 mg group.

Study 132 Tyramine Challenge in Parkinson's Disease Patients on LD

This double-blind placebo-controlled study assessed tyramine sensitivity (regarding blood pressure) pre- and post-treatment in Parkinson's Disease patients (on stable dose of LD/CD). Two groups (group 1 – rasagiline 1 mg QD; group 2 – rasagiline 2 mg QD) of subjects were studied sequentially and randomized to placebo (n = 3) or active drug (n = 6). Patients were studied for tyramine-induced pressor response to 75 mg tyramine pre-treatment and to increasing

doses of tyramine (up to 75 mg) post-treatment according to the study design shown in Figure 1. The rasagiline groups included 7 patients /group and the placebo group included 6 patients.

The subject was to take his/her assigned study medication and LD/CD dose and 30 minutes later, the patient was to be served a standardized morning meal in which tyramine has been mixed in applesauce and vital signs (blood pressure and pulse) were recorded at 5 minute intervals over the first 2 hours and at 15 minute intervals over the last 2 hours. The maximal systolic blood pressure and increment after tyramine were to be assessed and compared.

Figure 1 Study 132 Design

Visit	Screening	Screening	1	2	3	4	5	6	7	8	9	10	11
Day	- 2 weeks	-7	1	7	21	22	23	24	42	56	70	84	98
Tyramine		75 mg				25 mg	50 mg	75 mg			75 mg		
Tyramine restricted diet for 24 days													
Rasagiline (1 or 2 mg/day) or placebo were administered for 70 days													

Main Results

- Two patients (2 mg rasagiline group) were thought to have exhibited a rasagiline- tyramine interaction showing sustained systolic blood pressure increments after 50 mg and after 75 mg tyramine.
- The data did not suggest an effect of treatment on tyramine testing based upon mean maximal systolic blood pressure or mean maximal systolic blood pressure change. Mean ratios of maximal systolic blood pressure change for 75 mg tyramine at pre-treatment / day 70 did not suggest any treatment effect with mean ratios ranging between 2.1 – 2.5 for all 3 groups. Neither was there any suggestion for an increased frequency of systolic blood pressure increments of ≥ 30 mm Hg after tyramine at any of the tyramine challenges.
- Potentially clinically significant (PCS) abnormal orthostatic vital signs that occurred after tyramine and study treatment showed a highest frequency of hypertensive events (i.e. blood pressure increments > 30 mm Hg) in the 2 mg rasagiline group. Frequency of such events when occurring in the 1 mg group was typically greater than that in the placebo group.
- Review of PCS blood pressure readings from home ambulatory recordings did not suggest a clear effect of rasagiline on outlier readings, particularly for hypertensive events. Patients measured blood pressure twice daily (in am and randomly after dinner).
- Review of the adverse events (AEs) suggested that there may have been an increased frequency of AEs coded as hypertension related to rasagiline. Two patients treated with 2 mg rasagiline had 4 AEs, one patient treated with 1 mg rasagiline had 1 AE, and there were no such AEs in patients treated with placebo.

- There was a suggestion of increased orthostatic blood pressure measurements in rasagiline treated patients.

Tyramine Challenge Sub-Study 232 (TEMPO) “Early” Parkinson's Disease (Monotherapy)

Early Parkinson's Disease patients participating in the rasagiline monotherapy trial (232 - TEMPO) were studied for tyramine sensitivity at the end (6 months) of the randomized, double-blinded, placebo-controlled phase. Patients had been randomized to placebo (n = 17), 1 mg rasagiline (n = 19) and 2 mg rasagiline (n = 19) vital sign responses were assessed after 75 mg tyramine. The primary outcome measure was the # patients experiencing a systolic blood pressure increase of ≥ 30 mm Hg on 3 consecutive measurements compare to baseline (mean of 4 values).

After patients ate their own meal (without significant tyramine), they received 75 mg tyramine added to applesauce within an hour of the completion of their meal. The study meal was meant to simulate the subject's normal dietary habits.

Main Results

- No patients met the primary outcome measure but 2 patients (2 mg rasagiline) exhibited borderline pressor responses after tyramine that were just barely beneath the protocol-defined threshold.
- Mean maximal systolic blood pressure was 137, 148, and 153 mm Hg for placebo, 1 mg rasagiline and 2 mg rasagiline, respectively after 75 mg tyramine. Mean maximal systolic blood pressure increment was 15, 19, and 21 mm Hg for placebo, 1 mg rasagiline and 2 mg rasagiline, respectively.
- There was an increased frequency of subjects showing a systolic blood pressure increment of ≥ 30 mm Hg in 1 mg (21 %) and 2 mg (16 %) rasagiline groups compared to placebo (6 %). Only one subject (2 mg group) exhibited a systolic blood pressure increment ≥ 50 mm Hg (i.e. 51).

Tyramine Challenge Sub-Study 133 PRESTO (“Advanced” Parkinson's Disease on LD)

“Advanced” Parkinson's Disease patients participating in the rasagiline adjunctive trial (133 - PRESTO) were studied for tyramine sensitivity at the end (6 months) of the randomized, double-blinded, placebo-controlled phase. Patients had been randomized to placebo (n = 22), 0.5 mg rasagiline (n = 22) and 1 mg rasagiline (n = 13) vital sign responses were assessed after 50 mg tyramine. The primary outcome measure was the # patients experiencing a systolic blood pressure increase of ≥ 30 mm Hg on 3 consecutive measurements compare to baseline (mean of 4 values).

This study was generally conducted similarly as Tyramine Substudy 232 (TEMPO) with a major study design difference being that 50 mg tyramine was administered immediately at

the end of the meal during the dessert phase. Tyramine was also added to one of several dairy desserts instead of to applesauce as was done in the TEMPO Tyramine Substudy.

Main Results

- Four subjects (7%) had an increase in BP that met the predefined endpoint of systolic BP of > 30 mmHg above the mean baseline value for at least 3 consecutive measurements. Three of these subjects (# 4, 118, 266) had received 0.5 mg/day rasagiline and one had received placebo (# 411). None of the subjects who received 1 mg/day rasagiline had a clinically significant blood pressure increase during the tyramine challenge.
- Mean maximal systolic blood pressure was similar (141-146 mm Hg) among all treatment groups.
- Mean maximal systolic blood pressure increment above pre-tyramine baseline was higher in the 0.5 mg rasagiline group (27 mm Hg) than the mean value (21 mm Hg) for both the placebo and 1 mg rasagiline groups.
- Although the frequency of maximal systolic blood pressure increments was similar (17 – 24 %) among all treatment groups for increment \geq 30 mm Hg, there appeared to be an increased frequency of marked outlier responses \geq 60 mm Hg for the 0.5 mg rasagiline group (18 %) compared to the placebo (5 %) and 1 mg rasagiline (0 %) groups.
- Marked outlier responses in the 0.5 mg rasagiline group were exhibited by the 3 patients (patient # 4 - 69 mm Hg; patient # 118 – 78 mm Hg; patient # 266 – 69 mm Hg) who met the protocol-defined primary tyramine threshold outcome plus another patient (# 10 – 65 mm Hg) who did not. The single placebo patient (# 411) who exhibited a marked outlier increment patient (74 mm Hg) had also met the protocol-defined primary tyramine threshold outcome.

Reviewer's Overview of Tyramine Sensitivity Related to Rasagiline Treatment

- My perspective is that Study P94159 provides potentially the most useful, interpretable information on rasagiline-induced tyramine sensitivity (as a possible reflection of MAO-A inhibition). This study was conducted under fasting conditions and used a conventional approach of assessing tyramine threshold pressor dose responses (i.e. TYR30 or tyramine dose that increased systolic blood pressure by \geq 30 mm Hg) while administering increasing doses of tyramine before and after study drug treatment. However, this study was associated with numerous problems/limitations including : 1) relatively small number (N = 3-5) of subjects per treatment showing actual threshold responses; 2) extremely homogeneous study population (young healthy males) with probable bias for lowest rasagiline exposure (i.e. plasma rasagiline AUC) ; 3) concerns about the biological potency of tyramine; 4) narrow daily dose range (e.g. only 1 and 2 mg) for studying rasagiline; 5) absence of 25 mg tyramine dose that could provide more accurate assessment of TSF; and 6) DSI inspection report that

did not document evidence assuring protocol specified fasting and dietary restrictions and appropriate measurements of blood pressure. My recommendation is that a study employing a similar approach must be conducted with an improved study design to overcome problems and limitations identified for Study P94159 prior to approval.

Study P94159 suggested a modestly increased tyramine sensitivity (i.e. TSF = 2.8) associated only with the 2 mg daily dose (and not with 1 mg; TSF = 1.3). However, plasma tyramine measurements showing higher ratios after treatment than before treatment for both doses of rasagiline vs placebo also suggested some MAO-A inhibition by the 1 mg dose. **Based upon other PK data, there is a suggestion that increased plasma rasagiline exposure occurs in females, older subjects, patients treated with LD, subjects with mild hepatic impairment and patients using drugs inhibiting CYP 1A2 (e.g. a fluoroquinolone, fluvoxamine, ticlodpine, etc.) or drugs that are substrates of CYP 1A2 (e.g. caffeine, acetaminophen, amitriptyline, naproxen, propranolol, etc.) and could act as competitive antagonists that might increase rasagiline exposure. Thus, an elderly, female with hepatic dysfunction and treated with LD and 1 mg rasagiline and one or more interacting drugs (e.g. drugs that inhibit CYP 1A2 or compete as substrates of CYP 1A2) could potentially be exposed to a much higher AUC for plasma rasagiline (than the exposure observed in young, healthy males). Correspondingly, a patient experiencing an additive effect of several of these factors influencing rasagiline PK/exposure could potentially exhibit a significantly increased sensitivity for tyramine (i.e. potential hypertensive “cheese” reaction). A more comprehensive study as suggested ought to characterize the TSF more precisely.**

- I find it difficult to interpret the results of the 3 studies assessing tyramine sensitivity (e.g. pressor responses) in which relatively low doses of tyramine (50 or 75 mg) were added to food and administered to patients with Parkinson's Disease either just before or just after other food. The main problem is that food can markedly alter the bioavailability/PK (e.g. decrease C_{max} and AUC and delay T_{max}) of tyramine. The sponsor's rationale to administer tyramine with food was to represent a more realistic situation in life whereby a patient might be exposed to a “high” amount of tyramine contained within a meal (food and/or drink). Unfortunately, this is not a common approach to assess tyramine sensitivity by administering tyramine by adding it to food. There was no “positive control” MAO-A inhibiting drug that was simultaneously studied to show that this testing approach is reasonably sensitive for demonstrating the presence of absence of tyramine sensitivity.

I am not aware of unequivocal evidence/data indicating that the bioavailability of tyramine contained within a food/drink product is similar or different from that of tyramine added to food (and also administered either just before or after other food). **The sponsor did not validate its tyramine testing approach to assure the reviewer that the absence of significant tyramine-induced pressor response was a true negative and not a false negative resulting from a significant diminishing or abolishing effect of the food on the bioavailability of tyramine and correspondingly the pressor response of this tyramine.** In addition, the decreased monitoring in the design of these studies after 2 hours of tyramine administration could also have contributed toward missing significant tyramine-induced

pressor responses occurring not unexpectedly at a relatively late timepoint (e.g. after 2 hours). Nevertheless, the data accumulated in these studies suggest some rasagiline-induced increase of tyramine sensitivity. This suggested increase in tyramine sensitivity was not only observed at the 2 mg daily dose but also at a lower dose down to 0.5 mg daily. Considering that this study design could potentially underestimate an increase in rasagiline-induced tyramine sensitivity, it seems clearly noteworthy that any patients appeared to exhibit sensitivity to tyramine given the probability that tyramine bioavailability was significantly reduced and T_{max} was significantly delayed and therefore the study design did not seem ideal for characterizing a significantly increased sensitivity to tyramine-induced pressor responses.

- I recognize that the study design of administering tyramine under fasting conditions may not mimic real-life in which patients ingest tyramine containing. Nevertheless, this is the standard investigational approach for assessing the potency of a drug for increasing tyramine pressor sensitivity as a reflection of MAO-A inhibition. The absence of the confounding effects of food on tyramine bioavailability and corresponding pressor response allows one to characterize tyramine sensitivity and calculate the TSF. Once the TSF has been well characterized for different drug doses and the shape of the dose response curve has been established, then the next challenge is to interpret and assess the risk for a hypertensive “cheese” reaction based upon the TSFs, shape of the dose-response curve, and expectation of individual variability of drug exposure related to many factors and finally decide if dietary tyramine restriction is or is not desired.

I strongly believe that characterization of TSF based upon tyramine testing under fasting conditions should be the main method for assessing tyramine sensitivity. The sponsor should conduct a randomized, double-blinded, placebo-controlled larger study of both older males and females, study a wider range of rasagiline doses (e.g. 0.5 – 4 mg), compare selegiline as used in the U.S. (e.g. 5 mg BID), include lower doses of tyramine, and add a positive control group (e.g. tranylcypromine, non-selective MAO inhibitor). After such data have been accumulated, one could debate the utility of conducting additional, complementary testing of assessing tyramine sensitivity to doses of tyramine added to food. However, before initiating such studies, it would seem important for the sponsor to know more about the PK of tyramine when added to food under the sponsor’s design and the pressor responses of the this tyramine in untreated subjects and in subjects treated with a known inhibitor of MAO-A.

- Although there were some individuals who seemingly exhibited significant hypertensive responses to tyramine during tyramine testing, I am not aware that any of these experiences could be classified as “hypertensive urgency, emergency or crisis” because of the absence of significant symptoms (e.g. headache, chest pain, transient ischemic attack-like symptoms. Dr. Lisa Jones, however, did bring to my attention one patient’s experience(# 808) that I do think may represent a hypertensive “cheese reaction” associated with rasagiline treatment. There was a second patient (#803) in the same study who developed hypertension and headache on a high dose of rasagiline. Patient #803 did not clearly present as a patient experiencing a hypertensive “cheese reaction.” There is no way to be certain, but patient #808 could certainly be a hypertensive “cheese reaction” related to consumption of tyramine in her food

or drink and resulting from MAO-A inhibition related to the high dose of rasagiline. Both patients had participated in a small, tolerability, dose-escalation (1, 2, 5, 10 mg) rasagiline trial (Study TVP-1012/111). Because of cardiovascular events of these 2 patients and a third with postural hypotension, the protocol was amended to reduce rasagiline dosing to 1 mg/d. It I have presented narrative summaries of both of these cases with hypertension and headache after 10 mg daily treatment..

Patient #808 was a 58 year-old woman who participated in a dose-escalation (1, 2, 5, 10 mg) rasagiline trial (Study TVP-1012/111). This patient had a five year history of Parkinson's Disease and hypertension was not listed among her past medical history (asthma, appendectomy). At randomization the subject's medications were:LD/CD, selegiline, biperiden, bromocriptine, and alpha-tocopherol acetate.

This subject received escalating doses of rasagiline 1 mg/day (for one week), 2 mg/day (for one week), and presumably 5 mg/day in the third week as planned in the protocol. On day 22, the dose was increased to 10 mg/day in the fourth week. On day 25, the subject experienced vertigo for approximately one hour, and headache, nausea and vomiting which lasted for several days. The study medication was stopped for 48 hours beginning on day 25. **On day 28, the subject developed severe headache and hypertension (220/120).** A blood pressure "later on that day" was stated to be within normal range, without any pharmacological intervention. The subject's rasagiline dose was reduced to 2 mg/day. The events of day 28 led to the subject's hospitalization on day 29, which lasted ten days. The study drug was permanently discontinued upon her hospital admission. After admission, the subject reported headache, mild nausea and vomiting for nine days. Hypertension was reported to have been stabilized within six days of admission following treatment with captopril, which was continued for forty days. The subject then switched to methyldopa for ten days, and finally stopped all anti-hypertensive medications 52 days after the event occurred. From that time until the last follow-up visit (two months after stopping anti-hypertensive treatment), the sponsor reported the subject remained normotensive. No information was provided regarding the patient's recent diet with respect to tyramine containing foods preceding the severe hypertension. This patient's blood pressure measurements were normotensive, with standing measurements of 120/85 (Baseline), 120/80 (Week 1), 120/80 (Week 2), and 120/85 (Week 3).

Patient #803 was a 64 year-old female who had had Parkinson's Disease for 9 years. Her medical history was remarkable for suspected Raynaud phenomenon, S/P hysterectomy and oophorectomy. Her medications included LD/CD, selegiline, lorazepam, meprobamate, pravastatin, and alpha – tocopherol. Her selegiline was discontinued one month before she began taking rasagiline in the dose escalation design. She experienced localized muscle cramps/dystonia on day 1 and day 22, while being treated with rasagiline 1 mg/day and 10 mg/day, respectively. On study day 22, her rasagiline dose was raised from 5 mg/day to 10 mg/day.

On study day 28, the subject experienced headache and hypertension (160/110). Her dose was decreased to 5 mg/day, although these symptoms were reported to last for two days. The subject also reported onset of vertigo on day 28, which persisted for approximately ten days.

On study day 29, the subject experienced a syncopal episode lasting two minutes, which resulted in a one day hospitalization. During the hospitalization, "a high blood-pressure" was measured, and the subject was diagnosed with hypertrophic cardiomyopathy. The study drug was discontinued at this

time. The subject's blood pressure was reported to stabilize after two days treatment with propranolol and to remain within normal range until the end of the study follow-up period.

- There were 1452 Parkinson's Disease patients and healthy subjects (not including all clinical pharmacology studies) who had been exposed to rasagiline in the entire clinical program with or without LD and 1858 subject years of exposure has been accumulated. The majority of the rasagiline treatment experience in patients was not associated with dietary tyramine restriction. In Parkinson's Disease patients on LD and any dose of rasagiline without dietary tyramine restriction, the exposure was ~ 660 patient years. The sponsor had also noted that some patients had been on rasagiline and LD/CD for years without dietary tyramine restriction and without evidence of a rasagiline-induced tyramine reaction. However, it is relevant to consider that there could be some selection bias here because patients prone to significant AEs from rasagiline could discontinue from study and not be exposed to rasagiline for long periods.
- The sponsor did not consider that there was any event that could be considered a result of a potential tyramine/rasagiline interaction. **However, the sponsor has never defined what is a tyramine /rasagiline interaction.** The sponsor also noted that there were 65 patients on rasagiline 0.5 mg or 1 mg with or without LD and 29 patients on rasagiline 2 mg monotherapy who participated in tyramine challenge studies. These studies assessed the potential for interaction between rasagiline and tyramine after short and long term exposure "using very high and non-physiological doses of tyramine." The sponsor's overall conclusion based upon the results of these studies together with the results of home monitoring of blood pressure after meals was that rasagiline at these conditions is selective for MAO-B inhibition and can be used safely without dietary restrictions as monotherapy and as add-on therapy to LD at the indicated doses.

I differ from the sponsor's conclusion and think that some subjects treated with rasagiline and challenged with tyramine exhibited significant, asymptomatic, tyramine-induced hypertensive responses and that patient #808 (Study TVP-1012/111) may represent a classical hypertensive "cheese reaction."

Main Conclusions

- There are many concerns, limitations, and shortcomings for the conventional tyramine study (under fasting conditions) determining tyramine sensitivity (i.e. TSF) after treatment with rasagiline.
- The 3 other studies assessing tyramine sensitivity in Parkinson's Disease patients were confounded by the study design of administering tyramine with food and also just before or after other food. There was no validation of this method to assure that results did not underestimate tyramine-induced pressor responses.
- Some data suggest rasagiline-induced tyramine sensitivity not only with the 2 mg dose but also with lower daily doses (e.g. 0.5 and 1 mg).

There is a clear need for additional study to characterize more precisely and comprehensively rasagiline-induced tyramine sensitivity mainly by studying tyramine sensitivity under fasting conditions with an aim to overcome limitations and shortcomings of the previous study. **This study must be conducted prior to approval.**

Overall Conclusions

1. Rasagiline is effective for the treatment of the signs and symptoms of “early” Parkinson's Disease patients as monotherapy and for the signs and symptoms of “advanced ” Parkinson's Disease patients as adjunctive treatment.
2. The pharmacodynamic effect of rasagiline with respect to inhibition of MAO-A and the corresponding risk for causing a hypertensive “cheese” reaction (from ingesting dietary tyramine) has not been adequately characterized. This characterization must be conducted prior to approval.

Recommendations

Requirements for Approval

4. A randomized, double-blinded, placebo-controlled study (under fasting conditions) must be conducted to characterize the risk more precisely and comprehensively for rasagiline-induced tyramine sensitivity. Such a study should be designed to address the following concerns, problems, and limitations of the previous study :
 - 1) relatively small number (N = 3-5) of subjects per treatment showing actual threshold responses;
 - 2) extremely homogeneous study population (young healthy males) with probable bias for lowest rasagiline exposure (i.e. plasma rasagiline AUC);
 - 3) concerns about the biological potency of tyramine;
 - 4) narrow daily dose range (e.g. only 1 and 2 mg) for studying rasagiline;
 - 5) absence of 25 mg tyramine dose that could provide more accurate assessment of TSF;
 - 6) DSI inspection report that did not document evidence assuring protocol specified fasting and dietary restrictions and appropriate measurements of blood pressure.
5. Provide quantitative information of the effect of LD on rasagiline PK parameters/exposure.

Other Recommendations (Not Required for Approval)

1. Consideration should be given about conducting validated studies that assess tyramine sensitivity in rasagiline treated subjects when administered tyramine with food.

3. CLINICAL PHARMACOLOGY

3.1. Pharmacokinetics

In interpretation data and information about pharmacodynamic actions of rasagiline, it is important to have an understanding about the pharmacokinetics (PK) of rasagiline in human. For ease of reference in recalling and understanding relevant PK information about rasagiline, I have summarized the human PK information for rasagiline (from my original review) and conclusions of the review by the Clinical Pharmacologist / Biopharmaceutical Reviewer (Dr. Andre Jackson).

Summary of Human Pharmacokinetic (PK) Information

Eleven Phase I studies have been conducted by Teva to describe the human pharmacology and bioavailability/bioequivalence of rasagiline and its inactive metabolite, 1-Aminoindan (AI) following oral administration. There were 2 rich sampling drug-drug interaction studies for theophylline and ciprofloxacin. Nineteen other drug-drug interactions were investigated in the PRESTO study using sparse sampling and population analysis. An additional rich sampling study was completed to assess the potential interaction of rasagiline with tyramine.

Rasagiline was rapidly absorbed following oral administration, with T_{max} occurring at 1 hour post-dose in healthy subjects. Rasagiline is 90-94% protein bound in males and 88-92% protein bound in females (binding to human albumin is 61-66%) with red cell partitioning of 0.1-1.2 over the concentration range 1-100 ng/ml. Rasagiline is rapidly metabolized in the liver. In studies with human liver microsomes rasagiline was primarily metabolized by a single cytochrome P-450 enzyme, CYP1A2. Rasagiline's main metabolite, aminoindan (AI), is found in the urine and accounts for about 20% of the dose (less than 0.5% of the administered dose is excreted unchanged in the urine). The absolute bioavailability is 36%. Mass balance based upon radio-labeled drug indicated 60% and 7% respectively excreted in the urine and feces in one week, for an overall recovery of 84% in 38 days. There is no interconversion from the R to the S isomer. Figure 2 and Figure 3 show phase 1 and phase 2 metabolic biotransformations of rasagiline, respectively.

Figure 2 Phase I Biotransformations of Rasagiline

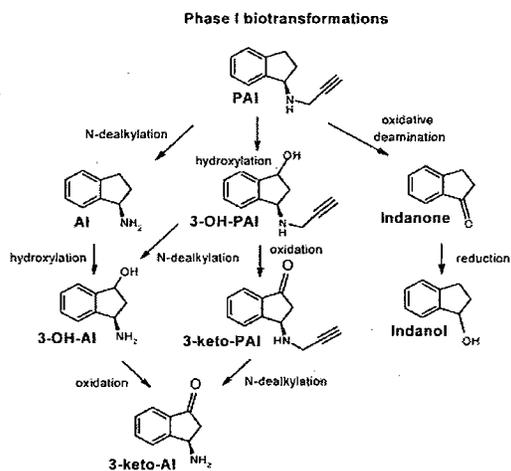
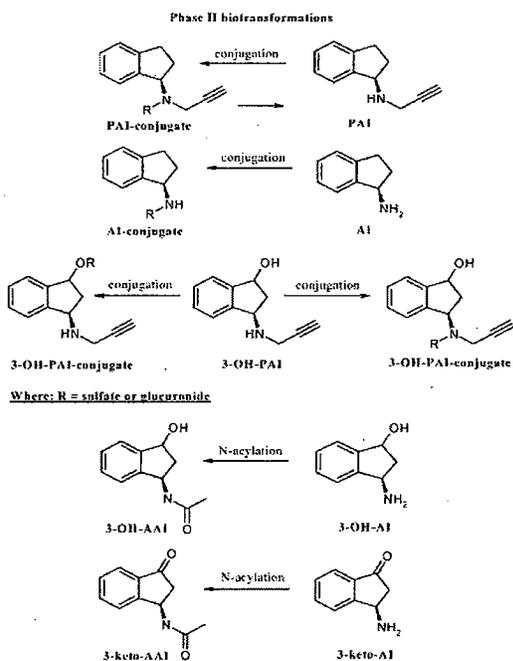


Figure 3 Phase II Biotransformations of Rasagiline



Multiple dosing studies in PD patients not on LD showed that the pharmacokinetics were linear from 1-4 mg/day. Another study done in PD patients with rasagiline being administered as adjunct therapy to LD/carbidopa exhibited linear kinetics over the dosage range of 0,5-2 mg/day.

In a multiple increasing dose (10-day, once daily doses of 2, 5 and 10 mg) study with 24 healthy subjects, no accumulation was found for rasagiline and the metabolite AI. Rasagiline $t_{1/2}$ (half-life) is between 2.1 ± 1.1 and 3.5 ± 1.5 hours and $t_{1/2}$ of AI is between 10.4 ± 2.2 and 11.6 ± 1.3 hours. The estimate of accumulation via was 1.0, assuming a half-life of 3 hrs. Rasagiline exhibits a departure from dose proportionality above 2 mg in normals in AUC for PAI and AI following a single dose administration at the dose range of 1-20 mg and also exhibits a decrease in clearance based upon time of exposure (i.e., Clearance is lower following multiple dosing).

There were no gender differences (i.e. > 2 fold difference between males and females) following 1 mg once daily dosing. **However, it should be noted that Dr. Jackson's perspective of a gender difference is a > 2 fold difference between males and females.** Population analysis indicated that CL/F would diminish 1% per year. CL/F increased with body weight, 0.4L/hr per kg of weight. Systemic exposure increased 7 fold for AUC_{tau} at steady-state between moderately hepatic impaired subjects and normals. Maximal exposure at steady-state was only two-fold different between mildly hepatic impaired subjects and normals. It is recommended that rasagiline should not be administered to subjects with moderate to severe hepatic impairment. Caution is advised in dosing patients with mild liver impairment. No dosage adjustment appears necessary in subjects with renal impairment since less than 0.5% of the dose is excreted unchanged in the urine.

Levodopa (LD) in the monotherapy Parkinson's Disease subjects resulted in a 31% decrease in rasagiline CL/F. However when LD was the substrate, there was no effect of rasagiline on LD.

There was an 83% increase in AUC for rasagiline in the presence of steady-state ciprofloxacin, an inhibitor of CYP1A2. There was no effect of rasagiline on theophylline or theophylline on rasagiline when they were co-administered. The results of the tyramine challenge studies indicated that rasagiline can be used safely without dietary tyramine restrictions. However several questions need to be addressed by the firm related to special populations, hepatic disease and ethnic groups. The increase in the TY30 ratio may be dangerously high in these groups and needs to be addressed by the firm due to the decrease in clearance in hepatic disease.

Rasagiline did not inhibit cytochrome P450 isoenzymes (at concentrations 3 fold higher than observed at the proposed 1 mg dose), CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A. These results indicate that rasagiline's therapeutic concentrations are unlikely to cause any clinically significant interference with substrates of these enzymes.

There was an increase in rasagiline clearance, at doses of 1.0 and 2 mg, of 39.1% in Parkinson's Disease subjects in the monotherapy clinical study who were currently smoking tobacco however this effect was not apparent in PD patients on chronic LD therapy that were smokers and received rasagiline 0.5 and 1 mg doses.

The concomitant intake of rasagiline with food decreased the C_{max} and AUC by 60% and 20% respectively.

The to-be marketed 1 mg tablet was determined to be bioequivalent to the clinically studied tablet.

Rasagiline dissolution was investigated in 3 pH ranging media and a dissolution method and specifications are being set in this NDA.

3.2. Pharmacodynamics

The most important pharmacodynamic issue of concern relates to the potentially increased tyramine sensitivity and risk of a hypertensive “cheese” reaction associated with rasagiline treatment. My Executive Summary in the Introduction/Background section outlined my initial pharmacodynamic concerns on this issue and the following section of the Sponsor’s Response to the Approvable Letter and my review of this submission provides further information on this same issue.

4. SPONSOR’S RESPONSE TO APPROVABLE LETTER SUBMISSION

4.1. Overview of the Sponsor’s Response and Format of My Review

The sponsor’s response to Agency concerns about rasagiline increasing tyramine sensitivity consists of 3 parts : 1) opinion of the sponsor’s experts; 2) the sponsor’s overview of all data in the rasagiline development program; and 3) the sponsor’s response to specific questions/comments made by the Agency in the Approvable letter. In this review, I have summarized arguments and/or data provided by the sponsor in regard to Agency concerns about increased tyramine sensitivity associated with rasagiline treatment. In some instances, I have provided direct quotes from the sponsor’s response. Following the various sections of the sponsor’s response, I have provided my comments on the sponsor’s response

My reviewer comments are interspersed throughout various sections of the sponsor’s response. The beginning of my comments are delineated by a subheading **(Reviewer Comments)** indicating the beginning of my comments for the specific section and ending with another subheading (End of Reviewer Comments) indicating the end of my comments for the specific section.

For the most part, the sponsor has reiterated data interpretations and arguments presented previously in the original NDA submission supporting the overall theme that there is no reason for concern about increased tyramine sensitivity to rasagiline and risk of hypertensive “cheese” reactions associated with rasagiline treatment \leq 1 mg daily. In addition, the sponsor’s response consists of specific arguments attempting to address Agency tyramine concerns outlined in the Approvable letter. In many instances, similar arguments are mounted repeatedly in different parts of the response including some that presented in all 3 parts. In some of these cases, I have not repeated the same data presentation but have merely noted that the same argument was mounted

in an earlier part and then referred to where the argument was mounted and/or have summarized the argument briefly.

The following text (in italics) is a quote abstracted from the Approvable letter outlining the Agency's concerns about the potential for increased tyramine sensitivity associated with rasagiline treatment.

**CLINICAL
TYRAMINE STUDIES**

"We are concerned that the selectivity of rasagiline 1 mg/day for MAO-B has not been adequately demonstrated in the 4 tyramine challenge studies provided in the NDA.

Although the Paris study appears, in form, appropriate to adequately assess rasagiline's selectivity for MAO-B, there are a number of flaws that make the results unreliable.

First, we note that numerous patients either met the blood pressure criterion only at the 800 mg dose of tyramine or did not meet the criterion even at that dose. In our experience (and that in the published literature), the vast majority of subjects in tyramine sensitivity studies respond to doses considerably lower than 800 mg, whether they are receiving treatment with study drug or placebo. The apparently poor responsiveness of these subjects raises serious questions about the interpretability of the results.

Further, the number of subjects studied was very small and the number of relevant subjects who reached the blood pressure criterion in both treatment periods was still smaller, making the results less than reliable. The use of young healthy males as subjects is an additional problem. We are concerned that older men and women might not only be more sensitive to the effects of tyramine, but that they would have higher plasma levels of rasagiline than younger patients, a problem if selectivity of rasagiline is incomplete (as suggested by the data, which suggest increased tyramine sensitivity at the 2 mg dose). For these reasons, we cannot be confident that results in young healthy males can adequately reflect the sensitivity of the relevant patient population to ingested tyramine. We also note that these studies typically use as a blood pressure criterion three consecutive systolic elevations of at least 30 mm Hg; in this study, only a single elevation was considered necessary and, as noted, this criterion was not regularly met.

We also note that you acknowledged that there were increased plasma levels of tyramine even after 1 mg treatment (vs placebo) and that this could be evidence for some degree of MAO-A inhibition.

In the three remaining challenge studies (Study 132, the TEMPO sub-study, and the PRESTO sub-study), the tyramine challenge was provided as tyramine mixed with food (e.g., applesauce, yogurt or ice cream) and administered in close proximity to a meal. There is no information available as to how the food with which tyramine was mixed affects tyramine bioavailability. We are thus not sure whether this represents a challenge comparable to a "high" tyramine meal in which there is significant tyramine bioavailability. The bioavailability of tyramine administered as a capsule can be markedly reduced if taken in the fed state and T_{max} is typically delayed. In summary, we are concerned that the patients who did not demonstrate significant tyramine-induced blood pressure increments represent false negative results because of poor tyramine bioavailability rather than true negative results.

Even if this concern could adequately be addressed, the results of these studies are unconvincing. In Study 132, safe passage in 6 patients at rasagiline 1 mg, although somewhat reassuring, is not definitive, especially given that the next dose of rasagiline tested (2 mg) was associated with a tyramine response in 2/6 patients. We also note the occurrence of tyramine reactions in three patients receiving 0.5 mg of rasagiline in the PRESTO study. Although we also acknowledge none of the 19 subjects in the TEMPO sub-study at 1 mg/day experienced tyramine reactions, none was on concomitant levodopa. The results of PRESTO might suggest that tyramine sensitivity is increased when rasagiline is taken concomitantly with levodopa. Finally, in all of these studies, the presumed delay in peak tyramine levels when tyramine is taken with food might have delayed the time at which the blood pressure criterion might have been met; unfortunately, the frequency of blood pressure measurements decreased after several hours, thereby increasing the possibility that any blood pressure elevations might have been missed.

For the reasons stated above, then, we request that you perform an adequate tyramine sensitivity study (randomized, double-blinded, placebo-controlled). Some important elements that the study should incorporate include:

- 1. Use of an appropriate number (e.g., - 20) of patients (e.g., equal number of older males and females; 40-70 years) receiving rasagiline as monotherapy.*
- 2. Use of an appropriate positive control treatment group.*
- 3. Use of a tyramine product demonstrated to be appropriately bioavailable, and tyramine should be administered in the fasting state.*
- 4. Use of multiple dose levels (e.g., 0.5, 1, 2, 3, 4 mg) of rasagiline, including doses that produce exposures approximately equal to the maximal exposures expected in patients receiving therapeutic doses of rasagiline (e.g., maximally metabolically inhibited, patients with mild hepatic insufficiency, or patients with multiple, factors separately resulting in an additive risk of significantly increased exposure, etc.).*
- 5. Use of an initial dose of tyramine of 25 mg, and dose increments above 100 mg of 100 mg up to 800 mg. Post-treatment tyramine should start at 12.5 mg because subjects could be very sensitive to 25 mg. Tyramine doses should be administered on separate days.*
- 6. Use of a blood pressure criterion of three consecutive systolic increases of at least 30 mmHg.*
- 7. Measurement of plasma tyramine at 30 minutes after each tyramine challenge (Y†† 25 mg) in all treatment groups pre- and post-treatment.*

If you choose to not perform such a study, you will need to include language in product labeling that informs patients and prescribes that patients must restrict their diet so as to avoid food with high tyramine content.”

The Sponsor Teva’s response to the tyramine issues consists of three parts, attached below :

Part 1. Evaluation of the Pharmacodynamics of Tyramine in Rasagiline Trials for the Treatment of Parkinson's Disease . An expert opinion by _____, and Ira Shoulson, MD, Professor of Neurology.

Part 2. Rasagiline Development Program Tyramine Overview of all data collected by the sponsor, demonstrating that dietary tyramine restriction is unnecessary at the clinical dose.

Part 3. Response to FDA action letter on tyramine issues.

The sponsor also included a document that was an overview of the sponsor's "Assessment of the Potential for Pharmacodynamic Interaction Between Oral Rasagiline and Oral Tyramine in Parkinsonian Patients and Healthy Subjects." This is the same document that been submitted in the original NDA. I did review this because this document had been reviewed previously in my original review.

The sponsor also submitted Appendix 2 that included tables of studies with pharmacokinetic (PK) data related to age and gender. Data from these tables were not separately reviewed but were discussed in the sponsor's responses and my comments to those responses.

4.2. Part 1 : Evaluation of the Safety of Rasagiline and Potential Tyramine Interactions in the Treatment of Parkinson's Disease (Opinions of Drs. _____ and Ira Shoulson)

The following summary in italics is a direct quote from the sponsor's response.

Summary

"Monoamine oxidase inhibitors (MAO-I) induce an increase in the bioavailability of tyramine, which can lead to short-term, marked increases in the blood pressure (BP) accompanied by reflex bradycardia and hypertensive urgencies and emergencies. There has been extensive evaluation of rasagiline, a selective MAO-type B inhibitor which has been developed for the treatment of Parkinson's disease (PD). Review of data from phase 2 and 3 studies, including 4 tyramine challenge tests, a large self-monitoring study of blood pressure (BP) in the PRESTO trial, and review of all adverse events of a cardiovascular during treatment revealed that: 1) no patient was characterized as having a hypertensive urgency or emergency in the rasagiline development program, 2) tyramine challenges did not show an increased pressor response in patients taking 0.5 and 1 mg of rasagiline, 3) 1 out of 20 patients on levodopa and 2 mg rasagiline had a consistent BP response to tyramine but without symptoms, 4) self-monitoring of the BP pre- and post-meal in a large number of patients taking levodopa and rasagiline at doses of 0.5 and 1.0 mg showed similar levels of increased BP on study drug

compared to patients on placebo. These data suggest that rasagiline did not have any clinically significant interaction with tyramine at therapeutic doses of 0.5 and 1.0 mg daily. In addition, no clinically significant interactions between tyramine and rasagiline at 2 mg daily were observed. This large database of experience in patients with PD supports the safety of administering a prescribed dosage of rasagiline without dietary restrictions."

The purpose of this report is to review the available data involving rasagiline and blood pressure to determine if there is indeed significant risk for hypertensive emergencies if patients are not cautioned to avoid tyramine-containing foods. The opinion of these experts reviews : 1) tyramine availability in food, 2) data from the pharmacodynamic interaction study between rasagiline and oral tyramine in study P-94159, 3) data from the 3 tyramine challenge studies performed in the USA (TVP-1012/132, TEMPO and PRESTO), 4) the findings from the self-monitoring of the BP in the entire PRESTO patient population pre and post-meals in an unrestricted dietary environment, and 5) evaluate the risk of cardiovascular events, including stroke, myocardial infarction, and cardiovascular deaths in patients in the rasagiline trials that were conducted without tyramine restrictions.

Tyramine bioavailability in food

In evaluating the pressor effects of tyramine when administered in food versus in capsules (with water, and presumably under fasting conditions-Reviewer's Note) at oral doses ranging between 25 and 75 mg, Bieck and Antonin (*J Neural Transm* 1989;28:21-31) demonstrated that systolic blood pressure responses were reduced by 60 to 98% in patients receiving reversible MAO inhibitors). Thus, maximal systolic blood pressure (BP) increases were not nearly as clinically significant as when the tyramine was administered in capsules. Other tyramine estimates in "very large meals containing substantial portions of meat, cheese, and wine," suggest that total tyramine content does not exceed 25-30 mg.

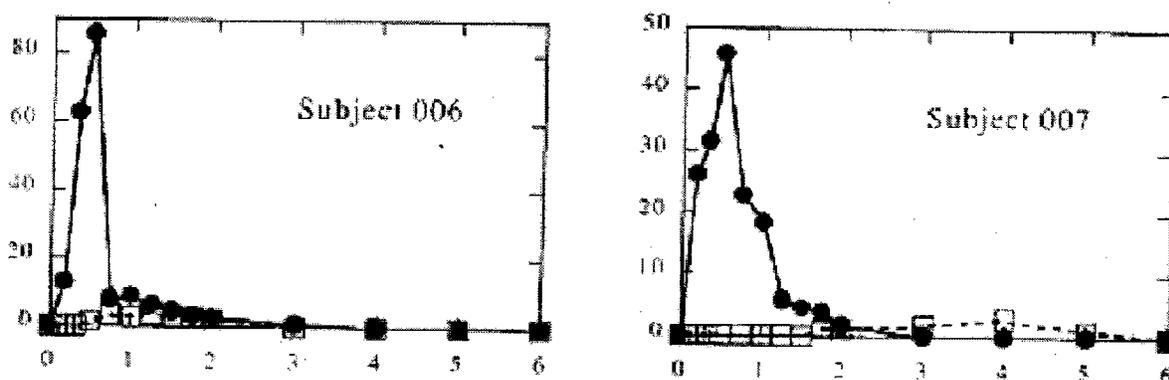
Since only 20-40% of the tyramine gets absorbed and in a more gradual fashion than pure tyramine in a capsule, the amount that is available with a 36 mg meal is probably closer to 8-16 mg. Thus, pressor studies evaluating the interaction between tyramine and selective MAO inhibitors do not require doses of tyramine capsules in excess of 25 to 50 mg to assess safety since patients with Parkinson's disease are highly unlikely to ingest more than 30 mg of total tyramine in a single meal, which would yield an estimated amount of 10 mg to 14 mg of available tyramine. As noted below, tyramine challenges in Parkinson's patients taking rasagiline at stable doses of 0.5, 1.0, and 2.0 mg daily utilized 25, 50 and 75 mg administered in applesauce or yogurt to maximize bioavailability. Thus, these doses were 2-6 times the amount that patients would ingest in a large meal with substantial tyramine content.

Reviewer Comments

- I essentially agree that a "high" tyramine meal is probably around 40 mg and does not likely exceed 50 mg. **However, the problem of disagreement occurs over the extent of change in bioavailability and change of kinetics of tyramine in a "high" tyramine ingestion (i.e. tyramine containing food or drink) and the effect of this significant**

change in tyramine PK on the pharmacodynamic (PD) (i.e. systolic blood pressure response). It is clear from many studies that the addition of tyramine to food results in a several important PK changes for plasma tyramine and blood pressure response to tyramine administered in this fashion. The changes (Figure 4) include :1) decreased bioavailability of tyramine with a marked reduction in AUC (mean ~ 70 %) and Cmax (mean ~ 80 %) (VanDenBerg et al., *J Clin Pharmacol*, 43:604-609, 2003.); 2) **delayed Tmax for plasma tyramine from 20-60 minutes to 30- 240 minutes**; and 3) alteration in “shape of the curve” from a clear peak to a much more flat curve without always a clear tyramine plasma peak. Other data show that administering tyramine to various meals (standard, or “high” lipid or protein rich meal) markedly delays the Tmax for tyramine and also may attenuate the blood pressure response by ~ 40 %, but the Tmax does not seem to change much according to the type of meal. If the Tmax changes by being delayed, then the peak PD pressor response would also be expected to be delayed.

Figure 4 Examples of Plasma Tyramine Pattern for Tyramine (250 mg tyramine HCl) Administered Under Fasting Conditions (closed circles and straight lines) and With a Meal (open squares and dashed lines)



- The sponsor’s approach in 3 studies was to add tyramine to applesauce or yogurt or frozen yogurt or ice cream and administer this tyramine challenge near a meal (just before or after a meal) that could alter the PK/PD of the tyramine challenge. Not only does the sponsor not know how each meal may have influenced the tyramine PK/PD, but the sponsor does not have any data about the PK/PD of the tyramine challenge when tyramine is added to applesauce or a dairy product. The sponsor argued that applesauce would not alter the bioavailability **based upon speculation (not data)** because applesauce did not alter the bioavailability of other drugs. I cannot agree with this speculation without any data showing the effect on tyramine PK/PD. It should also be noted that a comment (made by Dr. Temple) was given to the sponsor (at EOP2 meeting) to consider a tyramine challenge via a provocative meal containing tyramine. The sponsor did not want to follow this approach because of concerns about its ability to standardize such testing.

- **The sponsor has not validated in any way its rather unconventional approach (from a regulatory perspective) for characterizing tyramine sensitivity by administered tyramine with food and before and after other food.** Although I am aware that there are a limited number of publications that show results of blood pressure responses to oral tyramine administered with a meal after various drug treatments, I think that it is a stretch to say that this is an approach that it used to characterize a drug's effect on altering tyramine sensitivity. **I strongly consider the results of these studies involving tyramine administration with food and either just before or just after a meal to be of indeterminate significance in the absence of any validation of the sponsor's approach to confirm or suggest that the lack of a blood pressure response is a true negative.** The sponsor could have tried to validate its approach by showing how its provocative challenges affected (or did not affect) tyramine PK and blood pressure responses to this provocative challenge also possibly how such challenges affected responses in a positive control population (e.g. subjects with a certain extent of increased tyramine sensitivity from a drug known to inhibit MAO-A.)
- I think that it is also relevant to note that a study by Berlin et al. (*Clin Pharmacol Ther*, 46 : 344 – 351, 1989) clearly shows that subjects who have experienced MAO-A inhibition from moclobemide (200 mg TID) and reflect this inhibition with a moderately increased TSF (e.g. ~ 5) are not very sensitive to tyramine administered with food. The mean tyramine threshold of these subjects was 306 mg and ranged from 150 to 500 mg. Thus, it seems that even if rasagiline had produced a 5 fold increased sensitivity to tyramine as had been produced in this study by moclobemide, subjects might have required 150-500 mg of added tyramine (mean 306 mg) to a meal to respond with a tyramine threshold response of increasing systolic blood pressure by ≥ 30 mm Hg. I emphasize these observations in the context that subjects in the 3 tyramine challenge studies (adding tyramine to food and administering this near a meal) were administered a maximum of 50 or 75 mg tyramine added to food. Based upon knowing results of the publication by Berlin et al., I would not have expected a significant tyramine pressor response to 50 to 75 mg added unless tyramine sensitivity had been markedly increased and probably much more than a 5 fold increase in sensitivity.
- The sponsor's experts here also suggested that tyramine contained in cheese provokes an attenuated (~ 75 % reduction) blood pressor response compared to tyramine given without food (presumably in a fasting state). **However, I think that there are important caveats that should be emphasized (or at least recognized) with this study by Bieck and Antonin and the suggestion that tyramine in food may not be a very good stimulus to increase blood pressure.** The literature is not very extensive nor robust in terms of showing how frequently nor to what extent subjects show pressor responses to various ingested products containing tyramine (food or drink), particularly when MAO-A has been inhibited in such individuals. Neither is it known how reproducible pressor responses may be to ingestion of similar tyramine containing products at different times let alone under somewhat different conditions (e.g. other ingested products). It is also possible that ingestion of a liquid product (e.g. wine or beer) containing a significant amount of tyramine may provoke a significant hypertensive

response in a subjects with significant amount of drug-induced MAO-A inhibition. I am also not certain (based upon details in the publication) that the authors (Bieck and Antonin) had assessed maximal pressor responses to tyramine contained in cheese at potentially much later timepoints than when maximal responses were observed by administering tyramine in capsules. Finally there are a few studies showing that subjects with significant drug-induced MAO-inhibition may exhibit significant hypertensive responses to a provocative stimulus such as a meal containing tyramine (e.g. 65 mg).

In my view, there is a significant amount of research that could and should be done to clarify these many unknowns in this area. In the absence of additional data clarifying the many questions and concerns associated with conducting tyramine challenges with food/meals. **I think that it is best to rely on data derived from showing tyramine sensitivity under fasting conditions over a wide range of rasagiline doses including doses that mimic potential human exposures that could be achieved from various factors (e.g. age, gender, hepatic impairment, drug-drug interaction, etc.) that could increase exposure. If or when the presence of increased tyramine sensitivity has been shown and characterized, then one can assess the significance of this increased sensitivity relative to a potential need for dietary tyramine restriction.**

End of Reviewer Comments

Tyramine Challenge Studies in Subjects and Patients taking Rasagiline Study P94159.

This study was a pharmacodynamic interaction study between rasagiline (1 and 2 mg daily) or selegiline (10 mg daily) and oral tyramine in 27 healthy male volunteers. In this study, a classical design was utilized in which ascending tyramine doses were administered until the endpoint of a single elevation in systolic BP was reached. The methods to a certain positive tyramine reactions by the study investigator were appropriate. Doses of tyramine used were 50, 100, 200, 400 and 800 mg. Review of all graphs from the double-blind period showed that there were no pressor effects seen with 50 and 100 mg of oral tyramine in subjects taking 1 and 2 mg of rasagiline. The mean tyramine-30 ratio was similar for rasagiline 1 mg and placebo and for rasagiline 2 mg and selegiline 10 mg daily. Thus, this study showed no major pharmacodynamic effects with high doses of tyramine in subjects administered rasagiline at 1 and 2 mg daily.

Reviewer Comments

- My main concerns with tyramine challenge study P94159 conducted under fasting conditions were outlined in the Agency Approvable letter quoted earlier just prior to my description of the sponsor's overall approach to responding to tyramine sensitivity issues. This response appears to be merely a recapitulation of what was submitted originally by sponsor and does not seem to be an "objective," critical review of the

study recognizing/acknowledging or addressing specific shortcomings identified in this study and outlined in the Approvable letter.

End of Reviewer Comments

Tyramine challenges in TVP-1012/132, TEMPO (TVP-1012/232), and PRESTO (TVP-1012/133)

These studies evaluated the effect of tyramine in patients with Parkinson's disease. As shown in Table 2 below, the 132 study had 3 groups of patients (placebo, 1 and 2 mg of rasagiline) who were also on chronic LD therapy. In this study, no patient on 1 mg demonstrated an increase in systolic BP following administration of tyramine at 25, 50, or 75 mg. Two patients from the 2 mg dose group met the endpoint for a positive tyramine response at 25 and 75 mg, respectively, but neither were ever symptomatic. In one of these patients the response on 75 mg was not reproducible. The other patient who met the endpoint demonstrated highly variable blood pressures during ambulatory BP monitoring in the post-trial period.

Table 2. Findings from Tyramine Challenges in Study 132, TEMPO and PRESTO

Study	Levodopa	N	Doses (mg/d)	Patients with > 30 mmHg SBP increase (3 consecutive readings)*
TEMPO (232)	no	57	Placebo, 1, and 2	0
PRESTO (133)	yes	55	Placebo, 0.5 and 1 mg	3 on rasagiline and 1 on placebo
TVP-1012 (132)	yes	20	Placebo, 1, and 2 mg	0 on 1 mg dose 2 on 2 mg dose

* - no patient had a symptomatic increase in systolic or diastolic BP or a clinically significant reduction in the heart rate or changes in the electrocardiogram (ECG)

In the TEMPO study, 57 patients with Parkinson's disease who had been on placebo, 1, or 2 mg daily of rasagiline for 6 months (as monotherapy without LD) underwent a tyramine challenge test on the final day of the double-blind treatment period. No patients developed a pressor response to 75 of tyramine (Table 2).

In the PRESTO trial involving PD patients who were receiving LD and experiencing "on-off" motor fluctuations, 55 patients on placebo, 0.5 and 1 mg daily were studied in a challenge of tyramine 50 mg. In this study, there was one patient reached the pressor response endpoint on placebo, 3 patients on 0.5 mg of rasagiline and none on 1 mg of rasagiline. It is noteworthy that there were 2 other placebo patients who had elevations of ≥ 30 mmHg for 3 of 4 readings that were non-consecutive. Thus, the PRESTO trial did not show any increases in BP in Parkinson's

patients randomized to 1 mg daily and showed similar types of BP increases comparing patients randomized to placebo and 0.5 mg daily.

Reviewer Comments

- The sponsor's experts note that 2 asymptomatic patients (#206 and #209) treated with 2 mg rasagiline daily in Study 132 showed positive hypertensive responses to the primary outcome measure after tyramine administration. They also noted that the response was not reproducible in one patient (# 209) and that the other patient (# 206) who also exhibited a positive response showed "highly variable blood pressures during ambulatory BP monitoring in the post-trial period." However, they do not necessarily dispute the fact that this patient (#206) seemed to have demonstrated a hypertensive response to tyramine challenge. The sponsor also seems to acknowledge this possibility and this observation was not disputed in the meeting (9/27/04) with the sponsor. It is also of interest that patient #206 also appeared to show a higher PK rasagiline AUC exposure than expected in patients treated with 2 mg daily rasagiline. Thus, I think that this response in this patient (# 206) was a real response (i.e. true positive) to tyramine challenge.
- The sponsor's experts noted that no patients treated in study 232 showed a positive response to tyramine challenge. Although, technically I agree with this comment there are other observations that I think deserve comment. There were, however, 2 patients (2 mg rasagiline daily treatment) who exhibited borderline pressor responses after tyramine that were just barely beneath the protocol-defined threshold.
- Based upon additional analyses I conducted for Study 232 there was some suggestion of tyramine-related blood pressure increments. Mean maximal systolic blood pressure was 137, 148, and 153 mm Hg for placebo, 1 mg rasagiline and 2 mg rasagiline, respectively after 75 mg tyramine and mean maximal systolic blood pressure increment was 15, 19, and 21 mm Hg for placebo, 1 mg rasagiline and 2 mg rasagiline, respectively. There was also an increased frequency of subjects showing a systolic blood pressure increment of ≥ 30 mm Hg in 1 mg (21 %) and 2 mg (16 %) rasagiline groups compared to placebo (6 %). Only one subject (2 mg group) exhibited a systolic blood pressure increment ≥ 50 mm Hg (i.e. 51 mm Hg).
- I agree that one patient treated with placebo and 3 patients treated with 0.5 mg rasagiline daily in study 133 showed positive blood pressure responses to tyramine challenge. However, if this response in the rasagiline treated patients was real, it is somewhat puzzling that patients treated with 1 mg rasagiline did not also show responses as might be expected considering dose-response relationships. Although mean maximal systolic blood pressure was similar (141-146 mm Hg) among all treatment groups, it is of interest that mean maximal systolic blood pressure increment above pre-tyramine baseline was higher in the 0.5 mg rasagiline group (27 mm Hg) than the mean value (21 mm Hg) for both the placebo and 1 mg rasagiline groups. In addition, the frequency of maximal systolic blood pressure increments was

similar (17 – 24 %) among all treatment groups for increment ≥ 30 mm Hg, but there also appeared to be an increased frequency of marked outlier responses ≥ 60 mm Hg for the 0.5 mg rasagiline group (18 %) compared to the placebo (5 %) and 1 mg rasagiline (0 %) groups. Finally, marked outlier responses in the 0.5 mg rasagiline group were exhibited by the 3 patients (patient # 4 - 69 mm Hg; patient # 118 – 78 mm Hg; patient # 266 – 69 mm Hg) who met the protocol-defined primary tyramine threshold outcome plus another patient (# 10 – 65 mm Hg) who did not. The single placebo patient (# 411) who exhibited a marked outlier increment patient (74 mm Hg) had also met the protocol-defined primary tyramine threshold outcome. Altogether, these results from study 133 raise suspicions about rasagiline treatment and increased tyramine sensitivity but the lack of similar (or more severe) findings in the 1 mg daily group make it difficult to draw conclusions.

We do not have good information characterizing the shape of the dose-response curve for rasagiline related to its tyramine sensitivity and corresponding tyramine-induced pressor response. Conceivably, the tyramine-related pressor response could be similar for doses of 0.5 mg and 1 mg daily rasagiline (e.g. at the bottom of an S shaped dose-response curve) and the curve may start to rise sharply at 2 mg. Unfortunately, plasma rasagiline levels, that might provide some insight into the tyramine pressor responses observed in study 133, were not measured.

End of Reviewer Comments

Self-monitoring of the Blood Pressure in the PRESTO Trial

In the PRESTO trial, over 450 patients with longstanding Parkinson's disease treated with LD and experiencing "on-off" symptoms were randomized to placebo, 0.5 mg and 1 mg of rasagiline for 24 weeks. During the course of the study, an elaborate program of self-monitoring of the BP was performed at the baseline period, during the 3rd week of the study, and during the last week of the trial. Patients were trained by nurse coordinators to take BP at home before and at least twice daily (45 and 90 minutes) for 7 days after their main meal of the day. To help ensure data capture, trans-telephonic BP devices were used. These devices are hooked up to the patient's regular telephone line during the measurement and within seconds of completing the BP measurement, all of the data are transmitted to a central server for future analysis. As shown in Table 3, over 12000 BP measurements were made in *each* treatment group over the course of the study. The proportions of patients whose systolic BP increased by > 30 mmHg post-meal in the 3 study groups were similar and not statistically different. Furthermore, the number of patients who had severe (i.e., > 180 mmHg) increases ranged between 2.6% and 3.3% and was highest in the placebo arm ($p = ns$).

Table 3. Number and proportion of patients reaching a home endpoint after randomization in the PRESTO trial using a trans-telephonic monitoring device (5)

TVP- 1012/133 (PRESTO)	0.5 mg (N=153) 14,418 BP Readings		1 mg (N=138) 12,675 BP Readings		Placebo (N=152) 13,868 BP readings	
	N	%	N	%	N	%
Increase in SBP	33	21.6	23	16.7	28	18.4
Increase in SBP to > 180 mmHg	4	2.6	4	2.9	5	3.3

The data from this large BP monitoring study during the course of the PRESTO trial in which levodopa-treated patients without any dietary restrictions were studied demonstrate convincingly that rasagiline at doses of 0.5 and 1 mg daily did not increase the risk of post-meal hypertension compared with placebo.

Reviewer Comments

- In response to questions I posed, the sponsor has informed me that the total number of blood pressure readings shown for each treatment group above in Table 3 is erroneous. The numbers provided above in Table 3 relate to all safety data collected when the data could be identified (i.e. the ISS population/dataset) with a specific patient (i.e. the ISS population/dataset) but the analyses were conducted on a subset of patients (the Principal Data Cohort – PDC) and approximately 7000 readings/treatment group (~ 21,000 total readings) were excluded from the PDC cohort. In contrast, I was told that the data shown in Table 3 above were based upon a total of 9773, 8852, and 9213 readings (pre-meal and post-meal) per treatment group for the 0.5 (153 patients) and 1 mg (138 patients) groups and placebo (152 patients) group respectively that were collected after treatment. However, these total numbers included many pre-meal measurements conducted at home after treatment was initiated. Considering that the data presented for the incidence of systolic particularly threshold criteria (i.e. > 30 mm Hg blood pressure increments post-meal relative to pre-meal or a post-meal value > 180 mm Hg), the number of post-meal measurements is most relevant to know and should be provided.

I think that the presentation of the number of blood pressure measurements shown in Table 3 is somewhat misleading and gives the false impression that the incidence data shown in the table are based upon a much larger body of data measurements than they really were collected and analyzed after meals because baseline pre- and post-meal meal measurements and post-treatment pre-meal measurements are included in these numbers. The actual number of relevant blood pressure readings collected post-meal and post-treatment for the incidence data in the sponsor's Table 3 is therefore much less than the numbers (that include pre- and post-meal measurements at baseline and post-treatment) currently shown in this table. The number of post-meal measurements after treatment are actually 5849, 5200, and 5488 for the 0.5 and 1 mg rasagiline groups and placebo group, respectively.

- As presented these data in Table 3 derived from home blood pressure monitoring do not show a hypertensive blood pressure problem for post-prandial measurements. However, there are some important points to keep in mind regarding these data and some significant shortcomings in these data relative to any assessment that data exist that show that rasagiline treatment is not associated with significant increments in post-prandial blood pressure increments. The experts did not comment on the fact that the number of blood pressure readings shown in Table 3 is a significantly reduced subset of data from which many measurements have been excluded. Neither did the sponsor in its subsequent presentations and discussions of the home blood pressure monitoring data devote much attention to the limitations of these data considering the number of measurements excluded from analyses for various reasons and the limitations (e.g. relatively early time after eating) of when data were collected.

The sponsor's study report had noted that the primary analysis of blood pressure would consist of the Principal Data Cohort (PDC). The PDC excluded measurements : 1) without subject identification number; 2) taken at visits other than baseline (visit 0), week 3 (visit 1) or at termination (visit 6 – week 26); 3) taken during the meal; 4) taken > 60 minutes before meal 5) taken within 15 minutes post-meal; 6) taken > 180 minutes after end of meal; 7) taken without meal start or stop times; 8) associated with illogical meal schedule information; 9) considered "non-physiological" data (i.e. pulse pressure < 15 mmHg, or systolic BP > 260 mmHg, or diastolic BP > 140 mmHg, systolic BP < 60 mmHg, diastolic BP < 40 mmHg); 10) taken in which duplicate readings within 10 minutes exhibited extreme differences (i.e. difference in systolic BP > 60 mmHg, difference in diastolic BP > 30mmHg, pulse difference > 60 bpm). Duplicate BP measurements taken after the meal which were obtained within 10 minutes of each other were included in the Principal Data Cohort and subsequent statistical analyses. The mean of these duplicates was used in the statistical analysis of the primary safety end-point. The cut-off time of 70 minutes postprandial was used to define the first and the second time points of post-meal BP measurements and only 1 measurement (or acceptable duplicate) was allowed within the first (15-70 minutes) and second period (71-180 minutes). The number and reason for exclusion of measurements is shown in Table 1.

The PDC in the study report (as per the analysis plan) noted that there were 15,149, 13,523, and 14,175 blood pressure readings in the 0.5 mg and 1 mg rasagiline groups and the placebo group respectively. These total numbers included baseline and post-treatment measurement collected both pre-meal and post-meal. However, when the PDC was actually analyzed, additional measurements (not previously considered in the Statistical Analysis plan) were excluded when there were missing pre-meal and/or post-meal measurements. After these additional adjustments, there were 14,195, 12,520, and 13,232 blood pressure readings in the 0.5 mg and 1 mg rasagiline groups and the placebo group respectively and a total of 39,947.

- I think that it is also important to point out that the sponsor's original analyses of the PDC could potentially have excluded data that may have represented the hypertensive reaction that was being sought. For example, data that could have represented a hypertensive crisis because systolic blood pressure was > 260 mm Hg or diastolic blood pressure was > 140 mm Hg would have been excluded. Although no measurements of which I am aware were excluded because a systolic blood pressure measurement exceeded 260 mm Hg, many diastolic blood pressure measurements that exceeded 140 mm Hg had been excluded. It seems unlikely that such events could have occurred in the absence of symptoms that would have been associated with an adverse event. Furthermore, if there was a significant difference in "duplicate/replicate" measurements collected within 10 minutes, these data also could have been excluded. It is difficult to believe that blood pressure could rise so rapidly and so suddenly within 10 minutes. However, it is possible that markedly discrepant measurements could have been excluded because one replicate was a false low value in which case the real increment would have been excluded. In summary, it is difficult to dismiss the possibility that the sponsor's analytical approach could have excluded some data possibly suggesting meal-related blood pressure increments.
- I asked the sponsor to present the incidence data for significant post-meal blood pressure in a manner showing not only the post-treatment post-meal outlier data (that were shown in the sponsor's Table 3) but also showing these outliers at baseline, after treatment, and the difference or change from baseline after treatment (i.e. treatment % – baseline %) for the PDC with usable data. These results are shown in Table 2. These analyses show a greater treatment difference incidence (12.2 %) of a moderate post-meal systolic blood pressure increment (> 30 mm Hg to > 140) for the 0.5 mg rasagiline group compared to the 1 mg rasagiline (5.3 %) and placebo (7.7 %) for groups. In contrast, the treatment difference for the more "severe" post-meal systolic blood pressure increment (> 30 mm Hg to > 180) for the low dose rasagiline was slightly greater (2.0 %) than that of placebo (1.4 %) and the higher dose rasagiline was even greater (3.0 %) than those for both groups, suggesting some dose-dependence. These analyses indicate a treatment effect (rasagiline % – placebo %) of + 0.6 % for 0.5 mg rasagiline and + 1.6 % for 1 mg rasagiline. **Thus, these analyses might be suggestive of a rasagiline-related dose-dependent increased incidence of more severe meal related systolic blood pressure increments in particular at risk patients.**

Table 1 **Number of Records Excluded from PDC and Reason for Exclusion According to Treatment**

Description	0.5 mg N	1 mg N	Placebo N	All N
Total records obtained	-	-	-	66,144
Records missing patient ID #s	-	-	-	1,036
Records at other visit (not baseline, visit 1 or 6)	436	563	371	1,370
“Non-physiological” * records	288	220	261	769
Records missing some meal time	4,354	3,614	4,475	12,443
Records taken during meal time	414	400	410	1,224
Illogical meal schedule	0	0	2	2
Records > 60 minutes pre- meal	705	627	800	2,132
Records < 15 minutes post-meal	169	184	203	556
Records >180 minutes post-meal	353	224	333	910
Excessive records** in first & second post-meal period	764	664	642	2,070
Duplicates with “extreme” dif- ferences- SBP,DBP, or pulse***	146	187	137	470
Duplicates > 10 minutes apart in the same post-meal period	114	93	108	315
Total number of records excluded from total records obtained*	7,743	6,776	7,742	23,297
PDC (Total # – Excluded #) as per Analysis Plan	15,149	13,523	14,175	42,847
Records not usable because missing pre-and/or post-meal BP	954	1003	943	2900
Actual usable PDC	14,195	12,520	13,232	39,947

* “Non-Physiological” records = SBP ≥ 260 or ≤ 60, or DBP ≥ 140 or ≤ 40 or Pulse Pressure ≤ 15

**Only 1 record (or acceptable duplicate) allowed in first and second post-meal period (cut-off 70 minutes for first and second period)

*** “Extreme differences” = SBP > 60 or DPB > 30 or pulse > 60

- I also asked the sponsor to conduct similar analyses of the rate (# outlier post-meal increments/# measurements) of systolic blood pressure post-meal increments at baseline, after treatment, and the treatment difference (treatment result – baseline result). These analyses are shown in Table 3. The treatment difference of outlier event rate for moderate systolic moderate post-meal systolic blood pressure increment (> 30 mm Hg to ≥ 140) was similar in all 3 groups. However, the treatment difference was considerably higher for 0.5 mg rasagiline (+ 0.0017) and 1 mg rasagiline (+ 0.0006) compared to placebo (- 0.0002) for the more “severe” post-meal systolic blood pressure increment (> 30 mm Hg to > 180). **These analyses indicate a treatment effect (rasagiline rate – placebo rate) of + 0.0019 for 0.5 mg rasagiline and + 0.0008 for 1 mg rasagiline.** Although these increased treatment effects for the more severe increment are not dose-dependent, it is interesting to recall that the sponsor’s tyramine challenge data from this study (PRESTO)

had shown increased tyramine-induced systolic blood pressure increments in the 0.5 mg rasagiline group.

Table 2 Incidence of Pre-Meal and Post-Meal Hypertensive Events from Home Blood Pressure Monitoring at Baseline, After Treatment (visits 1 and/or 6) and Treatment Difference (i.e. Treatment % - Baseline %)

TVP-1012/133 (PRESTO)		0.5 mg		1 mg		Placebo		
Baseline (444 patients had data at baseline)	No. of readings	Pre-meal	1803		1577		1679	
		Post-meal usable	3236		2812		2936	
		All Usable	5039		4389		4615	
	No. of patients		157		140		147	
			N	%	N	%	N	%
	Increase in SBP¹		16	10.2	18	12.9	14	9.5
	Increase in SBP² to > 180 mmHg		2	1.3	1	0.7	3	2.0
Visit 1 and/or Visit 6 (443 patients had data post-randomization)	No. of readings	Pre-meal	3307		2931		3129	
		Post-meal usable	5849		5200		5488	
		All usable	9156		8131		8617	
	No. of patients		153		138		152	
			N	%	N	%	N	%
	Increase in SBP¹		33	21.6	23	16.7	28	18.4
	Increase in SBP² to > 180 mmHg		4	2.6	4	2.9	5	3.3
Treatment Difference (Rx – baseline) (Calculated only from the data of the 423 patients that had data at both baseline and at post-randomization (V1 & V6))	No. of readings	Pre-meal	4947		4303		4614	
		Post-meal usable	8811		7653		8111	
		All usable	13758		11956		12725	
	No. of patients		148		132		143	
			N	%	N	%	N	%
	Increase in SBP¹		18	12.2	7	5.3	11	7.7
	Increase in SBP² to > 180 mmHg		3	2.0	4	3.0	2	1.4

¹ Increase in SBP is defined as a post meal change of > 30 mmHg and SBP >140 mmHg

² Defined as a post meal change of > 30 mmHg and SBP > 180 mmHg

Table 3 Rate of Pre-Meal and Post-Meal Hypertensive Events from Home Blood Pressure Monitoring at Baseline, After Treatment and Treatment Difference (i.e. treatment rate and baseline rate)

TVP-1012/133 (PRESTO)			0.5 mg		1 mg		Placebo	
Baseline	No. of readings	Pre-meal	1803		1577		1679	
		Post-meal usable	3236		2812		2936	
		All Usable	5039		4389		4615	
			N	Event Rate	N	Event Rate	N	Event Rate
	Increase in SBP¹		50	0.0155 (50/3236)	47	0.0167 (47/2812)	51	0.0174 (51/2936)
	Increase in SBP to >180 mmHg²		4	0.0012 (4/3236)	3	0.0011 (3/2812)	7	0.0024 (7/2936)
Visit 1 and/or Visit 6	No. of readings	Pre-meal	3307		2931		3129	
		Post-meal usable	5849		5200		5488	
		All usable	9156		8131		8617	
			N	Event Rate	N	Event Rate	N	Event Rate
	Increase in SBP¹		111	0.0190 (111/5849)	97	0.0187 (97/5200)	115	0.0210 (115/5488)
	Increase in SBP to >180 mmHg²		17	0.0029 (17/5849)	9	0.0017 (9/5200)	12	0.0022 (12/5488)
Treatment Effect (Rx – Baseline)	No. of readings	Pre-meal	5110		4508		4808	
		Post-meal usable	9085		8012		8424	
		All usable	14195		12520		13232	
			N	Event Rate	N	Event Rate	N	Event Rate
	Increase in SBP¹		61	0.0035	50	0.0020	64	0.0036
	Increase in SBP to >180 mmHg²		13	0.0017	6	0.0006	5	- 0.0002

¹ Increase in SBP is defined as a post meal change of > 30 mmHg and SBP \geq 140 mmHg

² Defined as a post meal change of > 30 mmHg and SBP > 180 mmHg

- The sponsor's analyses of these data focused on the incidence of post-meal related systolic blood pressure increments in the PDC in individual and had excluded a large amount of data. I asked the sponsor to conduct additional analyses of a larger body of data including all post-prandial measurements collected at various time windows up through 800 minutes post-meal and also > 800 minutes and associated with a patient ID # and information allowing calculation of measurement with respect to a meal but not > 60 minutes pre-meal. "Replicate" data were to be averaged when these data were collected within 10 minute intervals. I also requested that various additional outlier criteria for systolic or blood pressure increments be applied and that these additional data be analyzed according to treatment group based upon the total number of individual measurements irrespective of the number of individual patients contributing to the data and also according to data characterized for each individual patient (e.g. incidence approach) by various averaging or techniques combining for an individual at each of the 3 collection times (baseline, week 3 or week 26. These requested descriptive analyses did not involve any calculations of statistical significance because of the multiplicity of various analyses and the exploratory nature of my requests. Overall, these requested analyses did not reveal any new obvious nor apparent differences suggesting hypertensive responses post-prandially compared to the original analyses.
- I consider a major shortcoming in these data requested data analyses is the fact that the focus on collecting measurements was on the early period rather than the later period after a meal. I have pointed out earlier the various data from adding tyramine to a meal that shows that peak tyramine levels and peak blood pressure responses occur at quite some time after a meal (to which tyramine has been added). The publication by Audebert et al. showed that peak pressure responses to a standard or lipid or protein rich meal (to which tyramine was added) at occurred ≥ 150 minutes in 83 % of the cases and at > 180 minutes in 65 % of the cases. Approximately 95 % of the measurements in each treatment group at each set of visits (baseline, week 3, week26) were collected within 150 minutes of the end of the meal. Correspondingly, only approximately 5 % of measurements across treatment groups were collected after 150 minutes and only ~ 2-3 % were collected after 180 minutes. Thus, it seems possible that if some patients were experiencing significant blood pressure increments from tyramine contained in their food, one might have expected these hypertensive responses to have occurred later than earlier. The study design imposed here did not seem sensitive toward collecting seemingly the most relevant data. Because the number of measurements at later timepoints was relatively small, it is not possible to draw any meaningful conclusions on these later data.
- It is also relevant to note that similar home blood pressure monitoring data were supposed to have been collected in Study 232 (TEMPO- monotherapy of early Parkinson's Disease involving 1 or 2 mg rasagiline daily vs placebo) based upon plans to amend the protocol to collect such data toward the end of the study. However, unfortunately for a variety of reasons, these data were never collected other than in a single patient. We suspect that 2 mg rasagiline daily clearly inhibits MAO-A to some extent (but we do not have a perspective on the quantitative extent, especially across many varied individuals. Thus, having home blood pressure monitoring data would have been highly desirable and very

important in potentially putting into perspective some “real life” tyramine eating exposure on this higher dose. If some patients taking rasagiline 1 mg daily have factors that increase their exposure to levels similar to patients taking 2 mg rasagiline daily without factors increasing exposure, it would have been helpful to have home blood pressure monitoring data from this study using this higher 2 mg daily dose.

End of Reviewer Comments

Cardiovascular Events During the Development of Rasagiline

Cardiovascular events reported during the entire rasagiline study program included fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, vascular emergencies, and hypertensive emergencies. As shown in Table 4, there was no increase in the incident rates of cardiovascular death on rasagiline versus placebo. There were also similar numbers of strokes and acute myocardial infarction for rasagiline versus placebo. There was one patient who had an aortic dissection and one who had a hypertensive emergency - both were randomized to placebo.

Table 4. Incidence of death and cardiovascular serious adverse events in TEMPO*, PRESTO, and LARGO (overall n = 1,563)

	Rasagiline** N=806 (% of patients)	Placebo/ Entacapone *** N=757 (% of patients)
Death (non-CV)	0	2 (0.4%)
Death (CV)	4 (0.5%)	6 (0.8%)
CVA	3 (0.4%)	3 (0.4%)
MI	4 (0.5%)	1 (0.1%)
Hypertensive and Vascular Emergencies	0	2 (0.3%)

* There were no serious CV events in TEMPO patients on 2 mg daily
** 0.5mg, 1mg, 2mg rasagiline
*** Including Placebo Run-in period

CV events -PHV data base, March 2003
Death

Reviewer Comments

- There were no apparent hypertensive crises (i.e. tyramine induced “cheese reactions”) in the safety experience to date at daily rasagiline doses of ≤ 2 mg. My original review had noted one case of subject receiving 10 mg daily who seemed to have a hypertensive “cheese reaction” crisis. The overall number of Parkinson's Disease exposed to any dose of rasagiline is 1361 as per the most recent Safety Update in this submission. Furthermore, the number of patients exposed to 2 mg daily is relative low (110) and relatively few patients (19) have received higher doses (4 or 10 mg daily). Thus, 1342 patients were exposed to daily doses of ≤ 2 mg daily. Using the “rule of 3” for assessing the maximal risk of a rare event, it would seem that the risk for a hypertensive “cheese reaction” at doses of < 2 mg daily is 3/1342 (0.2 %), and possibly much lower.

Based upon the most recent Safety Update, 62 % (1466 patient-years/2363 patient-years) of the rasagiline exposure was under conditions in which there was no dietary tyramine restriction. Thus, 38 % or 897 patient-years of exposure occurred with dietary tyramine restriction. Although most patients (95 % - 1288/1361) had been treated with rasagiline either as monotherapy or adjunctive therapy without dietary tyramine restriction at some time, the duration of treatment in these patients varied so that the exposure was much longer without tyramine restriction for some patients compared to others. Considering even if rasagiline treatment was associated with a risk for a “cheese reaction,” this risk ought to be markedly diminished during dietary tyramine restriction. Thus, if one assessed the maximal risk of patients who had been treated without tyramine restriction for any duration, “the rule of 3” would give a similar maximally limited risk (0.2 % - 3/1288) as calculated irrespective of tyramine restriction. These calculations only emphasize the possibility that the risk of tyramine-induced hypertensive “cheese reactions” could still occur with a significant, unacceptable frequency if rasagiline exposure without dietary tyramine restriction was permitted in a large population. Thus, the absence of detecting any “cheese reactions” in this extremely limited exposure experience is not necessarily that reassuring.

- I agree that the above review of cardiovascular events does not suggest an increased risk for rasagiline-treated patients with the possible exception of MI. I note that the relative risk for MI with rasagiline treatment was increased to nearly 4. I brought this to the attention of Dr. Lisa Jones who is doing the Safety review for rasagiline. It would be of interest to compare the rate of MI in these populations and also calculate the hazard ratio. If this is a real finding suggesting a real risk, I have no clear reason to suspect why such a risk may be associated with rasagiline other than possibly increased cardiovascular risk for MI associated with increased hypertension. However, I am not aware of any clear signal for increased cardiovascular risk with rasagiline based upon the Safety review conducted by Dr. Jones.

In her Safety Review of this submission including the Safety Update, Dr. Jones noted (Cardiovascular Events : Myocardial Infarction) that the sponsor had inappropriately

included a placebo-treated patient in the calculation of patients with MIs because the MI had occurred prior to randomization and treatment. Thus, the actual frequency of MIs is 0.5 % (4 rasagiline patients) vs 0 % (no placebo patients). Dr. Jones further discusses some problems with the sponsor's analyses and makes various comments but ultimately does not express a significant concern about rasagiline increasing the risk for MI based upon data from the development program.

End of Reviewer Comments

Conclusions

Rasagiline, a highly selective, irreversible, MAO-B inhibitor has been thoroughly studied during its development to detect clinically relevant interactions with tyramine in several different types of studies. The route of administration and the amount of tyramine used in the rasagiline development program were appropriately safe and simulated maximal and even supra-maximal tyramine intake in meals.

The pharmacodynamic studies of rasagiline do not show a clinically serious reaction to tyramine in patients on doses of 0.5 to 2 mg daily. Data in a small number of patients taking LD and rasagiline 2 mg show mixed results but no clinically harmful increases in BP were observed.

Perhaps the most clinically relevant data come from the self-monitoring of the BP in the PRESTO study, which has provided us with a very large database for post-meal changes in systolic BP in the absence of a dietary restriction during chronic treatment with rasagiline (0.5 and 1 mg daily) in patients on chronic levodopa. The outcomes in this study do not show any signals of clinically significant hypertension or its complications.

Based on our review of the effects of rasagiline on BP during tyramine administration and during clinical trials in PD patients treated with and without levodopa, we conclude that rasagiline can be safely administered without any dietary restrictions at a dose of 1 mg as monotherapy and as an adjunct to LD.

Respectfully submitted,



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Reviewer Comments

- I differ with the conclusions of the sponsor's experts.
- I think that risk for increased tyramine sensitivity has not yet been adequately characterized. The results of the tyramine study conducted under fasting conditions has many limitations and concerns that have been outlined. I also consider the results of the 3 tyramine challenge studies in which tyramine was administered with food and near a meal to be of indeterminate significance. There were many questions and problems associated with these studies. The absence of validation of this tyramine challenge approach to show that the absent responses represent true negatives rather than false negatives is a serious shortcoming.
- I think that there are many problems and limitations of the data collected, analyzed, and presented for the home blood pressure monitoring in study 133 (0.5 or 1 mg daily rasagiline vs placebo). Considering that important post-prandial blood pressure monitoring data are not available for the TEMPO study that treated some patients with 2 mg daily is also a notable shortcoming particularly with respect to the fact that increased tyramine sensitivity is suspected with 2 mg daily but the actual quantitative risk has not yet been well characterized.
- My conclusion remains that the inadequately characterized risk for rasagiline treatment requires that this risk be adequately characterized prior to approval with a well-designed tyramine challenge study under fasting conditions and including many of our recommendations. In the absence of the sponsor conducting such a study prior to approval, I conclude still that dietary tyramine restriction be required in the label for all rasagiline treatment.

4.3. Part 2 : Rasagiline Development Program Tyramine Overview of All Data Collected by the Sponsor, Demonstrating that Dietary Tyramine Restriction is Unnecessary at the Clinical Dose

Reviewer Comments

- The sponsor included an Executive Summary and also a summary of the Main Points Why Tyramine Restrictions Are Unnecessary in this part of the response. This

information is (presented in my Executive Summary at the beginning of this review. I will not comment on the sponsor's Executive Summary per se because I will deal with these comments on a point by point basis throughout my presentation of the sponsor's Part 2 as the sponsor makes specific arguments. However, I do want to point out an important inaccuracy noted by the sponsor in this Executive Summary. In point # 5 outlining why tyramine dietary restriction is not necessary, the sponsor interpreted the home blood pressure monitoring data from Study 133 (PRESTO) as reassuring when 1 and 2 mg rasagiline treatment was studied. **However, PRESTO did not study any treatment of 2 mg daily but rather studied 0.5 and 1 mg daily rasagiline vs placebo.**

End of Reviewer Comments

1 SELECTIVITY OF RASAGILINE

1.1 PRECLINICAL BACKGROUND AND DATA

The sponsor has summarized preclinical data supporting the potent, selective, irreversible nature of MAO-B inhibition with selectivity for inhibiting MAO-B as opposed to MAO-A. The rasagiline selectivity for MAO-B is noted to be comparable to that of another MAO-B selective inhibitor, selegiline which is approved for the treatment of PD patients in the U.S. without tyramine restriction.

Reviewer Comments

- I have no significant comments on this preclinical issue.

End of Reviewer Comments

1.2 NON-SELECTIVE MAO INHIBITORS AND TYRAMINE

It has been shown that in patients chronically treated with non-selective MAOI, as little as 10 to 20 mg of tyramine from cheese or other ingested food is capable of provoking a reaction accompanied by severe hypertension. In contrast, in a healthy individual not taking an MAOI, the amount of tyramine typically necessary to elevate the systolic blood pressure by 30 mmHg is approximately 500-1000 mg in a single dose. However, there is evidence that more sensitive individuals may respond in the presence of ≤ 200 mg tyramine. "In most studies involving the MAOI tyramine interactions in clinical pharmacology studies from the 1960s and 1970s, acute blood pressure elevations were classically observed between 40 minutes to 4 hours following the ingestion of tyramine or tyramine-containing food in MAO-Is treated individuals." During these earlier studies, a consistent rise in the systolic pressure of 30 mm Hg or more over baseline was arbitrarily designated as a positive pressor response to the study drug and tyramine

(or tyramine containing food) with or without accompanying elevation in diastolic blood pressure. Thus, during the past 30 years recommendations for patients on chronic therapy with the irreversible nonselective MAO inhibitors have been to avoid any protein food that is aging or spoiling and to prohibit certain other foods known to be high in tyramine content. With a selective MAO inhibitor such as selegiline, the amount of tyramine in food that will cause significant BP elevation is much higher.

Reviewer Comments

- With regard to MAO-B selectivity, it is clear that drugs purported to be MAO-B selective are only relatively selective and that this selectivity dissipates as the dose is increased. Selegiline, an MAO-B “selective” drug approved in the U.S. is a good example of this loss of selectivity with increasing plasma selegiline exposure. It is interesting to note that even for selegiline that there are no publications showing the risk for increased tyramine sensitivity based upon oral tyramine challenge studies conducted under fasting conditions and dose as per the U.S. label (10 mg daily as 5 mg BID). One unpublished study by the sponsor for selegiline (Somerset Pharmaceuticals) showed that the tyramine sensitivity factors (TSF or TYR30 pressor ratio) is approximately 2. Several other published studies of selegiline in different populations and under different conditions have suggested that the TSF for oral selegiline (≤ 10 mg daily) ranges from ~ 2 -3.
- Although there are many varied studied designs involving the assessment of tyramine sensitivity (i.e. TSF), my impression is that for the last 2 decades the majority published studies assessing TSF for various drugs have utilized a tyramine challenge under fasting conditions in which the pressor response to gradually increasing doses of tyramine is assessed. Some of these have conducted studies under conditions in which the tyramine is added to a meal or a provocative tyramine containing food stimulus has been used. However, from my assessment these studies are less frequent than the investigative approach under fasting conditions. Furthermore, studies involving tyramine challenge associated with food have usually been conducted to compliment data or information already accumulated in tyramine challenge studies conducted under fasting conditions.

End of Reviewer Comments

1.3 SELECTIVE MAO-B INHIBITORS AND LEVODOPA

In general, non-selective MAOIs affect the metabolism of number of drugs and may potentiate their effect. The risk for hypertensive crisis is higher when the patient receives an indirect sympathomimetic, causing the release of increased amounts of endogenous amines. In striking contrast to known non selective MAOI, selective MAO-B inhibitors at therapeutic doses (e.g. selegiline at ≤ 10 mg daily) do not cause profound and potentially lethal potentiation of the effects of catecholamines when administered concurrently with indirect sympathomimetic amines (e.g. dopamine), LD, or tyramine containing food or drink.

Reviewer Comments

- Although the sponsor did conduct a formal PK study assessing a potential effect of LD on plasma rasagiline from population PK analyses is suggested by one study in which there was a 31 % reduction in rasagiline clearance (i.e. increased rasagiline exposure). Another population PK study did not show a similar effect of LD on rasagiline. A formal PK study has not been conducted. Thus, in the absence of data settling this issue, I consider the possibility that concomitant LD treatment may increase rasagiline exposure somewhat, and potentially to a considerable degree if this occurs in the context of other factors increasing rasagiline exposure and the net effect is additive.

End of Reviewer Comments

1.4 USE OF SELECTIVE MAOIs

As MAO-A is the dominant form of the enzyme in the gut, liver and sympathomimetic nerve endings, the hypertensive crisis is attributed to inactivation of MAO-A. Therefore, inhibition of MAO-A explains the marked potentiation of tyramine caused by the irreversible MAO-A inhibitors or non-selective inhibitors. Reversible MAOIs or doses of irreversible MAO- inhibitors which maintain selectivity for the B-form of the enzyme are anticipated to lack the tyramine potentiation effect.

Moclobemide is a reversible and selective MAO-A inhibitor with short duration of action, efficacious in doses of 300-600 mg/day. Its improved tolerability profile in comparison to the classical nonselective MAOIs was shown particularly well by the absence of clinically relevant increases in the sensitivity to tyramine, obviating the need for dietary restrictions. Only a mild potentiation of the pressor response of tyramine was induced in combination with therapeutic doses of moclobemide; furthermore, this potentiation was virtually absent under natural conditions when tyramine is given in food. It has also been claimed that the interaction between tyramine in meals and toloxatone (another reversible MAO-A inhibitor) was unlikely to occur in patients after long term administration of the drug at therapeutic doses. This was a small study of 8 healthy volunteers, the dose of tyramine required to produce an increase of at least 30 mmHg in systolic blood pressure was lower (500 mg) in fasting state than in non-fasting state (1450 mg). During the administration of toloxatone, no significant increase in the systolic blood pressure was observed for tyramine doses of 200 mg or less.

Another reversible and selective MAO-A inhibitor is brofaromine efficacious at a dose range of 100-150 mg/day. Several studies performed with brofaromine demonstrated its favorable safety with respect to tyramine sensitivity measured the pressor effect of oral tyramine given either in capsules or the same amount in English cheddar cheese in 10 subjects during treatment with brofaromine (150 mg/day for 14 days). To measure increases of at least 30 mmHg in systolic blood pressure, the subjects received between 25-75 mg tyramine in capsules. The mean rise was 46 mmHg. The same amount of tyramine given in form of cheese caused a

mean rise of 11 mmHg, and in any case no more than 20 mmHg.

Audebert and colleagues studied the influence of food on the tyramine pressor effect during chronic treatment with moclobemide. In this study, subjects received 600 mg/day moclobemide. Starting from day 7 of treatment, the subjects consumed a standard meal into which tyramine was added daily in increasing doses until an increase of at least 30 mmHg in systolic blood pressure was obtained. Under these conditions, on moclobemide treatment a mean of 36.6 mmHg was obtained with 250 mg tyramine. The administration of the same amount of tyramine into a protein rich and a lipid rich meal significantly reduced the average increase in systolic blood pressure to 21 mmHg. It is evident from this study that increase in the lipid and protein content in food significantly attenuate the blood pressure increase. A large quantity of cheese would be required to provide a sufficient dose of tyramine to have the pressor response. It should be realized that this quantity of cheese would also provide a large amount of lipid that reduces the risk of blood pressure elevation.

Selective MAO-B inhibitors might also leave enough intestinal MAO available to prevent excess tyramine absorption. Indeed, selegiline (Eldepryl), is an *irreversible* and *selective* inhibitor of MAO-B. At a dose of 10 mg/day it is used both as an adjunct to levodopa and as monotherapy in the treatment of Parkinson's Disease patients without dietary restrictions. Elsworth and colleagues found no hypertensive response after tyramine (cumulatively 775 mg) was given orally to patients treated with selegiline up to 10 mg/day (Elsworth 1978). It is assumed, however, that tyramine sensitivity is increased during selegiline treatment at higher (20 mg or more) doses, when the drug becomes less selective and MAO-A also becomes inhibited.

Reviewer Comments

- The sponsor refers to some studies assessing effects of treatment with 2 reversible MAOIs and notes that these drugs resulted in an increased bioavailability of tyramine, presumably by inhibiting intestinal and hepatic MAO-A involved in first pass effect. Although an increased pressor effect and increased tyramine sensitivity was observed, the sponsor tends to emphasize that this was not important for possibly inducing a "cheese" reaction under normal eating conditions. However, the sponsor does not deal with some details of these investigations that impact on these complex issues and have potential implications.

In general, most investigations of which I am aware studying the potential effect of a MAOI drug on increased tyramine sensitivity (i.e. TSF) have focused on assessing pressor effects and not necessarily effects of the drug on tyramine bioavailability and relationship to these potential pressor effects. This potential interaction of MAOIs can get quite complicated because inhibition of MAO-A in intestine and liver and intraneuronal synapses can increase tyramine sensitivity but the important inhibition potentially mediating tyramine-induced "cheese" hypertensive reactions is likely associated with intraneuronal inhibition of MAO-A.

- The sponsor referred to various published investigations involving the assessment of a MAOI especially under conditions in which tyramine was contained in a food (e.g. cheese) or was added to food. In Part 1 (see Part 1, assessment of sponsor's expert consultants : Tyramine bioavailability in food section), I have presented my comments about publications and thus will not comment on them again.
- Although I tend to agree with the sponsor's comment that the selectivity of selegiline decreases at doses of ≥ 20 mg daily, I caution that not that there is relatively little investigation characterizing the shape of the dose response curve of selegiline (given BID) for TSF in a single study.
- I note here also that the sponsor acknowledges the fact that selegiline (10 mg/d) is used as adjunctive treatment with LD and also as monotherapy for Parkinson's Disease.

End of Reviewer Comments

1.5 TYRAMINE PLASMA LEVELS DHPG AND MAO-A INHIBITION

The sponsor described various data of MAOI inhibitors on catecholamine metabolism and noted that reduction of plasma dihydroxyphenylglycol (DHPG) can be used as a surrogate for inhibiting MAO-A and is considered the best pharmacological marker for MAO-A activity in humans. Reference to one publication (Radat et al., *Psychopharmacology*, 127 :370, 1996) noted that treatment with drugs that inhibit MAO-A always results in dose dependent reduction of plasma DHPG levels that is evident even after a single dose. Based upon these observations, the sponsor further observed that there was no difference in the pre- and post-treatment ratios of plasma DHPG for 1 or 2 mg daily rasagiline compared to placebo in Study P94159 (the sponsor's study assessing the effect of treatment on sensitivity to various doses of tyramine administered under fasting conditions).

The sponsor presented data noting that there may be small increments in plasma tyramine after treatment with moclobemide, a selective MAO-B inhibitor but that these levels are < 25 ng/ml and not associated with increments in blood pressure. The increments in ratio of plasma tyramine (at 1 hour post-tyramine) observed in Study P94159 for 1 and 2 mg daily rasagiline vs placebo were much less than 25 ng/ml. Reference to other publications noted that 34 ng/ml of tyramine resulting was associated with a small increased in systolic blood pressure and that much higher plasma tyramine is need to result in a systolic blood pressure increment of ≥ 30 mm Hg. Altogether these findings were interpreted as suggesting that inhibition of intraneuronal MAO-A is probably much more significant and relevant in the tyramine pressor response rather than plasma tyramine level. In contrast, isolated increments in plasma tyramine levels may reflect a change in intestinal tyramine metabolism and absorption related to inhibition of intestinal MAO-A rather than inhibition of intraneuronal MAO-A.

Reviewer Comments

- The sponsor notes that rasagiline treatment did not reduce plasma DHPG and based upon the suggestion that this is a good index of inhibition of MAO-A activity, the sponsor seems to imply that there is no reason for concern about rasagiline and MAO-A inhibition. I emphasize that I am not aware of data showing that this index (i.e. measurement of changes in plasma DHPG or any other catecholamine metabolic biomarker) is more sensitive index of increased tyramine sensitivity and increased pressor effects. If such was the case, I doubt that so much focus and investigation would be placed on assessing tyramine pressor responses after treatment with a MAOI. In the absence of compelling metabolic biomarker data to the contrary, I consider that assessment of tyramine pressor responses to increasing tyramine doses under fasting conditions is a more sensitive index of increased tyramine sensitivity to MAOI treatment than measurement of plasma and/or urinary catecholamine metabolic biomarkers.
- The sponsor comments that the increments in relatively low plasma tyramine levels in Study P94159 associated with rasagiline treatment likely reflects a decrease in intestinal tyramine metabolism and absorption related to inhibition of intestinal/hepatic MAO-A. The sponsor does not think that these mild increments in plasma tyramine reflect a significant risk for increased tyramine pressor effects and “cheese” reactions as would inhibition of intraneuronal MAO-A. I tend to agree with the sponsor’s view and do not think that these mild increments by themselves are a reason for concern. It is also noteworthy that the sponsor’s assessment of drug effect on plasma tyramine was not comprehensive involving multiple sampling over time but was focused upon a single timepoint for plasma sampling.

End of Reviewer Comments

1.6 COMPARISON OF THE MAO-B SELECTIVITY OF RASAGILINE AND SELEGILINE

It seems relevant to compare the results of tyramine interaction studies obtained with rasagiline to those found with selegiline. The comparison may enable the extrapolation of relatively limited clinical pharmacology data existing for rasagiline to real life situations, as selegiline (10 mg/day) has been used for years both as monotherapy and as add on to LD without any dietary restriction. The sponsor compared data for rasagiline with data obtained from Study P94159 and the literature with regard to tyramine sensitivity as reflected by TYR30 ratio (tyramine threshold to increase systolic blood pressure ≥ 30 mm Hg pre-treatment/ tyramine threshold to increase systolic blood pressure ≥ 30 mm Hg post-treatment). In Study P94159, subjects taking rasagiline 1 mg/day showed the same effect as those who were treated with placebo, namely no tyramine potentiation at all, whereas in subjects treated with selegiline 10 mg/day a slight increase of tyramine sensitivity was observed. Rasagiline at 2 mg/day (twice the clinical dose) was comparable to 10 mg/day selegiline (the clinical dose). None of the subjects had reached the threshold endpoint at a tyramine dose of < 200 mg, under fasting conditions. This finding further supports the selectivity of rasagiline to MAO-B and its safety in real life situation as such amount of tyramine can not be possibly achieved in food.(and moreover,

tyramine in food is 3 times less bioavailable). The TYR30 ratio for 10 mg selegiline daily was ≤ 2 in various publications.

In study P94159, plasma levels of DHPG in subjects receiving rasagiline (1 mg and 2 mg) were not different from those found in subjects on placebo. Plasma concentrations of DHPG in subjects treated with selegiline 10 mg/day were decreased, indicating a potential slight inhibition of MAO-A by selegiline and none with rasagiline.

Reviewer Comments

- I do not think that a comparison of effects on selegiline and rasagiline on TSF across studies is very useful. In contrast, I think that it is important to compare these drugs in the same study. In the only study (P94159) in which this was done, the mean TSF was 1.25 for 1 mg rasagiline (N = 4), was 2.80 for 2 mg rasagiline (N = 5), and was 4.33 (N = 3) for selegiline (10 mg QD). However, these data are based upon very small numbers of healthy male subjects who exhibited protocol required pressor increments. Although these data suggest that 2 mg daily rasagiline may be associated with a similarly increased sensitivity to tyramine as is selegiline (10 mg QD), and that there is no significant increase in sensitivity to 1 mg rasagiline daily, I view these data as very preliminary and not very definitive. It is desirable to obtain robust data that show the rasagiline dose response curve (up to at least maximally projected exposures, ? at least up to 4 or 5 mg) for many subjects (e.g. ~ 15 completers/treatment group) and especially older males and females. Such a small number of "homogeneous" subjects/group does not facilitate data due to genetic variation nor other factors age, gender that may contribute to an increase tyramine sensitivity for rasagiline. Conducting the study DNDP recommended in the Approvable letter would allow the sponsor to collect data that would permit a reasonable comparison of rasagiline with selegiline and the much desired, reasonably comprehensive characterization of rasagiline-dependent sensitivity to tyramine.

End of Reviewer Comments

1.7. SELECTIVITY IS MAINTAINED FOLLOWING LONG TERM EXPOSURE TO RASAGILINE

To further strengthen the evidence that under conditions mimicking real life, rasagiline at clinically relevant doses will not increase tyramine sensitivity, two tyramine challenge sub-studies were incorporated into the North American pivotal studies (monotherapy and adjunct to LD). In both studies, a high dose tyramine challenge was performed following 6 months of treatment to allow for a long term exposure to rasagiline in order to test the selectivity after long time treatment.

The tyramine was given with a light meal to create more realistic conditions although still more extreme than in real life allowing for high bioavailability (lipid/protein content was much lower than in a real tyramine rich meal although the doses of tyramine were as high as

in a very rich tyramine meal or even higher). Under these conditions, none of the patients had tyramine pressor effect as was predefined in the protocol. There was some variability in systolic blood pressure in 2 patients treated with 2 mg/day (twice the clinical dose) but it was not consistent with a tyramine reaction and did not meet the endpoint (study 232a - monotherapy). In study 133a (adjunctive to LD), 4 patients had increases of ≥ 30 mmHg in systolic blood pressure (3 on rasagiline and one on placebo, similar to the 2:1 treatment ratio between rasagiline and placebo). Additional 2 placebo patients had similar blood pressure increase but did not meet the pre-defined endpoint (because the increases were not in a sequence of 3 consecutive measurements, as defined in the protocol). These tyramine challenge studies demonstrated that elderly patients treated chronically with clinical doses of rasagiline have no increased sensitivity to tyramine doses that are much higher than those achievable with a very high tyramine containing meal.

Reviewer Comments

- I have described my concerns for the sponsor's approach about assessing long-term rasagiline-induced tyramine sensitivity by challenging patients with tyramine added to food and administering this challenge near a meal. My concerns have been outlined in my respective comments in Part 1 (see sponsor's expert consultant assessments under sections : Tyramine bioavailability in food and Tyramine challenges in studies 132, 232 and 133). I have not repeated my comments and concerns again here.

End of Reviewer Comments

2 RASAGILINE SAFETY IN REAL LIFE CONDITIONS

2.1 HOME BP MEASUREMENTS BEFORE AND AFTER MEALS

During the entire pivotal study 133 (PRESTO, adjunct to LD in North America) the patients underwent very intensive monitoring of their BP in relation to meals. They had to complete home blood pressure measurements before and after meals and record them as well as the food content in diaries during three different periods. These were: seven consecutive days prior to the baseline visit, to the week 3 visit, and to the week 26 (termination) visit. The blood pressure was measured by the patients employing a transtelephonic device which transmitted the results directly to a central reading center with an immediate alert if needed. Measurements were taken in duplicates before and 45 and 90 minutes after the main meal of the day. In addition, the patients had to fill in a special diary that recorded the content of the meal. The DSMC (Data Safety Monitoring Committee) reviewed the data in a cumulative manner in cohorts of 60 patients. Throughout and until the completion of the study, the DSMC did not identify any sign of risk that could affect or compromise the patient's well being. Analysis of BP levels prior to, and during study before and after meals in 472 patients in a real life setting showed that the BP fluctuation episodes were evenly distributed between treatment groups. This finding implies that episodes of hypertension following a meal may occur randomly and irrespective of MAOI treatment.

Event of BP increase was pre-defined as "an increase of 30 mmHg or more in systolic BP and above 140 mmHg". Event of severe increase in BP was defined as "an increase of 30 mmHg or more in systolic BP and above 180 mmHg". The sponsor presented the same table (Table 3) describing the distribution of post meal BP increases between treatment groups at any time after randomization as was shown earlier in Part 1 (opinion of the sponsor's experts). Based on this extensive database it is clear that rasagiline treated patients (on top of LD) have no increased sensitivity to pressor effect of tyramine in food even after a long term treatment.

In Study 132 as well, in addition to the inpatient tyramine challenges, all patients were supplied with a digital blood pressure monitor for self measurement of the daily blood pressure. The patients were instructed on the use of the BP device and completed a daily BP diary. Blood pressure measurement was performed twice daily: in the morning following study medication and regular LD/CD treatment and then in the evening after dinner. Blood pressure was taken while sitting, after five minutes rest and using the same arm throughout the study. The BP measurements derived from these diaries showed no clinically significant variations. Throughout the study period (including the period where tyramine diet was not required), three patients had single episodes of systolic blood pressure values exceeding 180 mmHg. These included 2 placebo patients (#106 and #108) and patient #206 on 2 mg rasagiline.

Reviewer Comments

- I have presented my comments and concerns about the reliability of the home blood pressure monitoring data earlier in my comments in Part 1 (see sponsor's expert consultant response section : Self-Monitoring of the Blood Pressure in the PRESTO Trial). I will not repeat them here again.
- The sponsor also referred to the lack of any significant signal from the data of patients who monitored home blood pressure in study 132. These data are not very helpful because only a very small number of patients were studied. A total of 20 patients were treated in 3 treatment groups (N = 6 or 7/group). Neither did there appear to be any systematic collection of data at a particular time post-meal in this study.

End of Reviewer Comments

2.2 EXPOSURE TO UNRESTRICTED DIET AND AE PROFILE

In the entire clinical program, 1452 Parkinson's disease patients and healthy subjects (not including clinical pharmacology studies) have been exposed to rasagiline with or without LD and 1858 subject years of exposure have been accumulated. All patients in pivotal studies and the vast majority of PD patients in the entire clinical program (95% ,1273/1346) did not have to restrict their diet of tyramine for a certain period of time during treatment (according to the protocol). A total of 58% (1072/1849.5 years) of exposure to rasagiline (0.5 mg, 1 mg, 2 mg)

were without tyramine restriction: 660 years on adjunct therapy and 412 years on monotherapy. Approximately 1140 patients have been treated with rasagiline for a period of at least 4 months without tyramine restrictions. Of these, about 267 patients were on 2 mg rasagiline. About 392 of these patients were treated with rasagiline as monotherapy and more than 745 in adjunctive to LD treatment. None of these patients had any event that could be considered a result of a potential tyramine/rasagiline interaction. The adverse event profile, both cardiovascular and general, was similar between rasagiline and placebo/ comparator treated patients in all studies conducted in both Europe and USA. Moreover, serious cardiovascular events such as CVA, TIA and MI were equally distributed between rasagiline and placebo groups.

Although it is evident that the general as well as the CV profile of adverse events is similar between patients treated with rasagiline and placebo, it is recommended that patients with mild hepatic failure (that may cause up to twofold increase in rasagiline blood levels) or those who take ciprofloxacin (a CYP 1A2 inhibitor that may increase rasagiline blood levels similarly) to administer 0.5 mg rasagiline as an additional safety measure.

Reviewer Comment

- I have presented my comments and concerns about the occurrence of cardiovascular and hypertensive events earlier in my comments in Part I (see sponsor's expert consultant response section : Cardiovascular Events During the Development of Rasagiline). I will not repeat them here again.

End of Reviewer Comment

3 TYRAMINE BIOAVAILABILITY AND FOOD

There were 2 types of tyramine challenge studies in the rasagiline clinical program, those which were under fasting conditions and those which tried to reflect real life conditions by administering tyramine near or with a meal and possibly with applesauce, yogurt, frozen yogurt, or ice cream. Extreme challenge of tyramine (fasting conditions and very high tyramine doses) is not considered medically safe in elderly patients treated with levodopa and therefore, the original intention of this design was to challenge the patients with tyramine doses exceeding those that might be consumed in real life and under fed conditions. In real life situations, the only source for tyramine is food, especially food rich in lipids and proteins. Administration of tyramine in such food reduces by about 3 fold the bioavailability of tyramine compared to fasting condition. Moreover, Audebert et al. (*Eur J Clin Pharmacol*, 1992;43:507) showed that 250 mg tyramine together with a clinical dose of moclobemide (a reversible MAO-A inhibitor) in a lipid-rich meal causes 50% less elevation in SBP than the same amount of tyramine in a standard meal (1000 kcal; 43g proteins, 52g lipids, 86g carbohydrates; total weight of meal 750 g). In Study 132 the patients received the tyramine mixed with an applesauce, and before meal. Applesauce does not contain lipids or protein, but is made up mostly of water and some carbohydrates. Therefore the extent to which it affects the bioavailability of tyramine is minimal, if any. The 2 patients (#206 and #209) in this study that had shown asymptomatic BP elevations, on a dose

two fold higher than the clinical dose (2 mg) were exposed to unrealistic conditions (fasting and extremely high doses of tyramine). To illustrate this, if the bioavailability of tyramine is increased by 3 fold when given on an empty stomach and the pressor effect in this study was seen at tyramine doses between 50-75 mg with rasagiline 2 mg, then to achieve the same effect one must consume a meal containing between 150-225 mg tyramine when treated with rasagiline 2 mg. All the more so if tyramine is given with 1 mg rasagiline, then the safety ratio is doubled.

It is well documented that tyramine content in a rich tyramine meal rarely exceeds 40 mg. In TEMPO and PRESTO, the tyramine was given after a light meal. In TEMPO the patients ate a meal of their own choice which consisted of a sandwich, a fruit/vegetable, a soup or cereal and in PRESTO patients consumed a low tyramine containing meal that they had brought from home. The light meal consisted of a sandwich, a beverage and a piece of fruit, or the equivalent. This was followed by dessert consisting of 6 to 8 ounces of yogurt, frozen yogurt or ice cream (according to the subject's preference) which was mixed with the contents of a capsule of tyramine hydrochloride. It can clearly be seen that this light meal does not resemble by any means even a standard meal, of course its lipid and protein content is extremely low in comparison to a rich meal. Therefore, the addition of high amount of tyramine to the light meal used in our study can be considered as a high exposure to tyramine. In a study by Berlin et al. (*Clin Pharmacol Ther*, 1989;46 :344) in which tranylcypromine 20 mg/day was given to healthy subjects after a 1000 Kcal meal and the contents of a tyramine capsule were mixed with in frozen yogurt, all subjects had a pressor response (mean tyramine dose to elicit response 35 mg, range 20-50 mg). In another study tranylcypromine 10mg/day was given to subjects receiving 250 gm of cheddar cheese containing 65 mg of tyramine. In this study all subjects had response to tyramine in this fed state with elevations in systolic blood pressure ranging from 75 to 100 mm Hg. In one patient, phentolamine had to be administered to stabilize the patient (Korn 1986). It is clear that with non-selective MAO inhibitors even a meal high in lipid/proteins is not enough to prevent the occurrence of tyramine response at low tyramine doses.

One could have argued that the administration of tyramine with food might have delayed the peak tyramine plasma levels and as a consequence might have also delayed the time at which the BP criterion might have been met, implying that the observation period was not long enough. The typical tyramine response evolves between 40 minutes to 4 hours (which in the time frame of our observation period). In effect when the time to peak SBP increase is compared with fasting conditions vs food (standard and high lipid/protein meal) there is a delay observed with food, but it is not beyond the 4 hour observation period (Audebert 1992). The frequency of BP measurements of every 15 min after 2h is considered adequate to detect any delayed tyramine response as its duration if appearing is always longer than 15 min. The protocols for both the Presto and Tempo challenge studies check blood pressures every 5 minutes for the first 2 hours and then every 15 minutes for the hours two to four. However, the protocol for both studies state that if a single elevation in SBP of ≥ 30 is observed, then monitoring would occur at every 5 minutes again. This procedure in the protocol ensured that no potential late occurring elevations in SBP were missed. In addition, as stated above, the content of the meals taken by the patients was not heavy enough to cause a substantial delay in absorption.

Reviewer Comments

- I have described my main concerns regarding the issue of how food can affect tyramine bioavailability and complicate the sponsor's tyramine challenge studies. My major concerns have been outlined in my respective comments in Part 1 (see sponsor's expert consultant assessments under section : Tyramine bioavailability in food and Tyramine challenges in studies 132, 232 and 133). I have not repeated my comments and concerns again here.
- The sponsor commented that "Extreme challenge of tyramine (fasting conditions and very high tyramine doses) is not considered medically safe in elderly patients treated with levodopa" is not considered medically safe. Although I can appreciate this overall perspective, it is possible that increasing doses of tyramine could be administered safely to "healthy" elderly subjects under fasting conditions **if there was close, careful blood pressure monitoring at frequent intervals (e.g. 5 minutes) AND the tyramine dose was gradually increased and not abruptly increased between intervals** (e.g. not > 100 mg increments as the dose is increased, or possibly even smaller increments such as 50 mg as the target tyramine dose becomes more substantial).

It is well known that there may be substantial PK/PD differences for various outcome measures between the elderly (e.g. ≥ 65 years old) subjects and non-elderly (< 65 years old) subjects. However, I am not aware that there are any data that show that the tyramine sensitivity resulting from treatment with a MAOI is greater or lesser in the elderly subjects compared to non-elderly subjects. I do not think that this issue has ever been investigated. What may be more important than studying elderly subjects vs non-elderly subjects would be to project for any increased rasagiline exposure that could occur on the basis of age and by ensuring that such increased exposure levels (related to PK differences) are covered by an adequate rasagiline dose range in a fasting tyramine challenge study.

- The sponsor referenced publications noting that patients challenged with 35 or 65 mg tyramine added to food or contained in cheese had significant pressor responses. However, I think that this is somewhat misleading because these responsive patients had been treated with 10 or 20 mg tranylcypromine daily, a non-selective MAOI that markedly increases tyramine sensitivity (usually > 20 fold TSF increase). It is not reasonable to expect that subjects treated with rasagiline might exhibit a significant pressor to such doses of tyramine administered under non-fasting conditions unless the tyramine sensitivity was markedly increased. There is no reason to expect that rasagiline treatment as relatively low doses (1 or 2 mg daily) would result in such a marked increase in tyramine sensitivity as occurs with ≥ 10 mg tranylcypromine daily.
- I had noted earlier (Part 1, see sponsor's expert consultant assessments under section : Tyramine bioavailability in food) that I considered sponsor's speculation that applesauce does not decrease tyramine bioavailability because it does not significantly decrease the bioavailability of other drugs when added to applesauce to be unconvincing. I also

emphasize that there are no data that show the presence or absence of an effect of yogurt, frozen yogurt, or ice cream on the bioavailability of tyramine added to these foods. This maneuver is potentially complicated by then consuming this tyramine added food near another meal. The sponsor argued that yogurt, frozen yogurt, or ice cream is not similar to a standard meal or lipid or protein rich meal that may be associated with decreased tyramine bioavailability and delayed time to pressor response. Again, the argument is not very satisfactory because it is based upon speculation rather than data.

- The sponsor noted that if a blood pressure reached the threshold (≥ 30 mm Hg systolic blood pressure increment) at a time during which the monitoring frequency was reduced, the more frequent monitoring (e.g. 5 minute intervals) would be reinstated. This comment was made to counter a DNDP comment that the sponsor's decrease in the frequency of blood pressure monitoring (at > 2 hours after tyramine challenge) might have missed demonstration of the primary pressor outcome (3 consecutive systolic blood pressure increments ≥ 30 mm Hg).

I think that it is still possible that the sponsor's study design could have missed the demonstration of a primary pressor outcome measure when blood pressure monitoring decreased to 15 minute intervals. Assuming that a measurement (called "time" 0) occurring after 2 hours does not represent a systolic increment of ≥ 30 mm Hg, the next measurement would not occur until 15 minutes later. If the next 2 blood pressure measurements that could have been made (but were not) occurred at 5 minute intervals (+ 5 and +10 minutes after "time" 0) were ≥ 30 mm Hg, and the measurement at a 15 minute interval was a systolic blood pressure increment ≥ 30 mm Hg (and the successive measurements at 5 minute intervals were not ≥ 30 mm Hg), the primary pressor outcome would not have been captured by measuring blood pressure at 15 minute intervals but would have been captured if blood pressure was monitored routinely at 5 minute intervals. Monitoring blood pressure at hourly intervals (as also occurred later during monitoring in TEMPO/232 and PRESTO/133) after "closer" earlier monitoring at 5 or 15 minute intervals would also be more susceptible toward missing significant blood pressure increments that could define an achieved threshold pressor response.

- I also note that even if the later, decreased blood pressure monitoring frequency was not an issue because the monitoring frequency occurred at 5 minute intervals, it is possible that tyramine-induced systolic blood pressure increments may not have met the primary outcome measure. This could have occurred because the food to which tyramine had been added or taken just before or after a meal may have attenuated or decreased the pressor response as has been shown in the scientific literature.

End of Reviewer Comments

4 PATIENTS EXHIBITING PRESSOR RESPONSE

The 2 patients (2 mg, Study 132) that had BP elevation during the tyramine challenge study, had also severe fluctuations in blood pressure, unrelated to rasagiline or to the tyramine

challenge. Patient #206 was monitored for 24 hours to assess blood pressure changes and showed marked blood pressure variations even in the absence of rasagiline. After review of BP curves by a cardiology consultant, his opinion is that subject 209 is not representative of a tyramine response.

In PRESTO, 4 patients met the end-point for 3 consecutive > 30mm Hg BP elevation. Three were on 0.5 mg and one was on placebo. It is important to remember, in this regard, that the randomization in this study was 2:1 (rasagiline:placebo). There was no dose-response and none of the patients on 1 mg showed any sign. In addition, 2 additional patients on placebo were identified as having some pressor signal, but this pressor signal did not reach the pre-defined end-point. These patients were on placebo. It is well documented that fluctuating PD patients have great variability in BP while switching between “on” and “off” states. In these patients the mean systolic-diastolic blood pressure, both supine and standing, is significantly higher during the “off” phase, as compared to the “on” phase. As patients in PRESTO have no baseline tyramine challenge - this could explain in part the elevations seen in BP.

In light of the fact that there are several conditions in which the plasma levels of rasagiline may be higher than the upper normal variation in patients administering the clinical dose, it is recommended that these patients (hepatically impaired or treated with CYP 1A2 inhibitory medications) will take 0.5 mg/day. This measure is assumed to provide the required safety margin.

Reviewer Comments

- I have provided my interpretations of the data for patients exhibiting pressor responses to tyramine challenge earlier in Part 1 (see sponsor’s expert consultant responses/assessments under section : Tyramine challenges in studies 132, 232 and 133). I have not repeated my comments and concerns again here.
- When considering my interpretations about pressor response to tyramine challenges, I also refer the reader to my comments and main concerns regarding the issue of how food can affect tyramine bioavailability and complicate and potentially confound the sponsor’s tyramine challenge studies. My major concerns have been outlined in my respective comments in Part 1 (see sponsor’s expert consultant responses/assessments under section : Tyramine bioavailability in food).
- The sponsor made a comment how patients who are “hepatic ally impaired” or taking a CYP1A2 inhibitor may experience a doubling of exposure (e.g. AUC) and should thus use 0.5 mg rasagiline daily (presumably expecting levels to be similar to those in subjects taking 1 mg daily and without hepatic impairment or a metabolic inhibitor of CYP1A2). This comment seems to acknowledge the sponsor’s sensitivity that if a 1 mg daily dose was used in such patients that an exposure similar to 2 mg daily (patients without hepatic impairment or CYP 1A2 metabolic inhibitor) would be expected and these patients could have an increased tyramine sensitivity and be at a somewhat increased risk for a “cheese”

reaction. The DNDP labeling in the Approvable letter had recommended dietary tyramine restriction for patients with hepatic impairment or inhibitors of CYP1A2.

End of Reviewer Comments

5 CONCLUSIONS

Based on the arguments discussed above and on the attached detailed response to the FDA approvable letter below, the Sponsor believes that the administration of rasagiline 1 mg/day with and without levodopa is safe in PD patients and does not require tyramine restricted diet.

Reviewer Comments

- I disagree with the conclusion of the sponsor that 1 mg rasagiline daily (with or without LD) is safe and does not require tyramine dietary restriction. Based upon the scanty, preliminary data available, it is premature to draw this conclusion
- Based upon the data available, I do not necessarily I think that a clearly unacceptable risk for increased tyramine sensitivity has been demonstrated and that tyramine dietary restriction cannot be avoided with rasagiline treatment. Instead, I believe that the risk for increased tyramine sensitivity and “cheese” hypertensive reactions has not yet been adequately characterized. I did not note that any significant new data were presented in any of the specific parts of the whole response. Neither did I find that the sponsor presented any new nor compelling argument supporting the perspective that rasagiline treatment (≤ 1 mg daily) is safe and acceptable without tyramine dietary restriction without first conducting the required study characterizing effects of rasagiline on tyramine sensitivity much more comprehensively.

The results of the tyramine study conducted under fasting conditions has many limitations and concerns that have been outlined. I also consider the results of the 3 tyramine challenge studies in which tyramine was administered with food and near a meal to be of indeterminate significance. There were many questions and problems associated with these studies. The absence of validation of this tyramine challenge approach to show that the absent responses represent true rather than false negatives is a serious shortcoming.

- I think that there are many problems and limitations of the data collected, analyzed, and presented for the home blood pressure monitoring in study 133 (0.5 or 1 mg daily rasagiline vs placebo). Considering that important post-prandial blood pressure monitoring data are not available for the TEMPO study that treated some patients with 2 mg daily is also a notable shortcoming particularly with respect to the fact that increased tyramine sensitivity is suspected with 2 mg daily but the actual quantitative risk has not yet been well characterized.

- My conclusion remains that the inadequately characterized risk for rasagiline treatment requires that this risk be adequately characterized prior to approval with a well-designed tyramine challenge study under fasting conditions and including many of our recommendations. In the absence of the sponsor conducting such a study prior to approval, I conclude still that dietary tyramine restriction be required in the label for all rasagiline treatment.

End of Reviewer Comments

4.4. Part 3 : Sponsor's Specific Point by Point Responses to Agency Concerns Outlined in the Approvable Letter

"In the approvable letter of Agilect dated 2 July 2004, the FDA expressed its concern that the selectivity of rasagiline 1 mg/day for MAO-B has not been adequately demonstrated in the 4 tyramine challenge studies provided in the NDA. We would like to address the Division's concerns about the selectivity of rasagiline 1 mg/day for MAO-B in our answers below by providing additional insight and clarifications and emphasizing few aspects that were included in the submission (see Appendix 1), but the Sponsor felt they deserved additional attention. The goal of this response document is to address the Agency's concern that the selectivity of rasagiline 1 mg/day for MAO-B has been demonstrated during the clinical program and to convince the Agency that rasagiline could be approved without tyramine dietary restrictions."

The following are responses to the agency's comments on the tyramine issues in the NDA :

1 SUBJECTS MEETING THE BP CRITERION IN STUDY P94159

The agency is concerned by the fact that many subjects in this study met the BP criterion at 800 mg of tyramine only and several of the subjects did not meet the BP criterion at all. The agency stated that from literature as well as from their own experience, most of the subjects respond at a considerably lower dose of tyramine. Indeed, the variability in the individual response to a tyramine challenge is not small. The sponsor refers to several studies noting that subjects studied for tyramine responses had been selected based upon exhibiting a TYR 30 response (i.e. typically systolic blood pressure increment at a particular tyramine threshold dose or lower. A reference to a publication Cooper (Brit J Psych, 1989, 155 : 38) noted that tyramine dose for producing a TYR 30 response may be > 500 mg under experimental conditions and > 1000 mg "in a real-life situation" (but there is not documentation as to the source of data for this statement).

It has already been described by Cooper et al, 1989 and Berlin, 1989 that in a healthy individual not taking an MAOI, the amount of tyramine typically necessary to elevate the systolic blood pressure by 30 mmHg is approximately 500-1000 mg in a single dose. However, there is evidence that more sensitive individuals may respond in the presence of 200 mg tyramine or less.

To reduce the variability of response, in many studies the investigators pre-screen the volunteers to receive a response to tyramine at a range of between 200-600 mg or even limit the range of response for included subjects to 400 . 600 mg at baseline. In some cases even the prescreened subjects do not respond to the higher tyramine levels. Four representative examples, out of many, are the following : (1) Antal and colleagues in their study aimed to compare the effect of oral linezolid with that of moclobemide and placebo on the pressor response to oral tyramine, allowed to enter the treatment period only those subjects who had a pre-treatment PD30 of more than 200 mg and less/equal to 800 mg. (2) In another study performed by Audebert and colleagues, the authors measured the effect of food on tyramine pressor effect during chronic moclobemide treatment. Here again, subjects who showed insufficient reaction to 600 mg tyramine dose and those whose test proved positive (increase of > 30mmHg) with the 200 mg tyramine dose, were excluded to reduce variability of the study. (3) Hinze C., Kaschube and Hardenberg described a study conducted in healthy volunteers with a new irreversible MAO-B inhibitor (MDL 72974A). They reported that subjects were eligible for inclusion if they had responded with an increase in SBP of at least 30 mmHg following 400 or 600 mg of tyramine. They were excluded if their pressure-response to 200 mg of tyramine exceeded 30 mmHg (over responders) or if at 600 mg the 30 mmHg increase was not attained (non-responders). In this study, nevertheless, 3 out of 24 subjects failed to respond during the study to a 600 mg tyramine challenge. (4) In a study to assess the tyramine pressor effect during treatment with Befloxatone (reversible MAO-A inhibitor) in healthy volunteers, the authors reported on a pre-screening, 7 days before the start of the study, to reduce the variability of the study population with regard to tyramine sensitivity. Only subjects whose fasting Tyr30 was obtained after oral administration of 400 or 600 mg tyramine were included in the study.

In Study P94159, twenty-seven subjects completed the study. Of these, 20 (74%) reached TYR30 at tyramine exposures ranging from 100 (subject 616) - 800mg in period 1 (tyramine alone) and 23 (85%) at exposures ranging from 50 (subject 1611-according to strict TYR30 definitions) to 800 in period 2 (treatment + tyramine). In contrast to the many studies in the literature, tyramine sensitivity was not screened for in the enrollment phase and there was no selection of subjects based on their response to tyramine challenge. Consequently, our study results should not be expected to attain as high a percentage of TYR30 responders as those referred to in the agency's letter. The non-screening protocol used in P94159 better simulates real-world conditions and thus increases its generalizability.

Reviewer Comments

- The Approvable letter pointed out to the sponsor that the vast majority (18/27) of subjects in study P94159 required ≥ 800 mg threshold doses (systolic blood pressure increment ≥ 30 mm Hg). Whereas 11 subjects required a very high tyramine dose (800 mg) to meet the tyramine pressor threshold, 7 subjects presumably required higher doses because they did not meet the threshold response at dose up to 800 mg. In responding to this comment, the sponsor referred to some studies involving screening of subjects for their tyramine sensitivity before studying selected subjects who have met a certain, defined threshold response (e.g. systolic blood pressure increment ≥ 30 mm Hg). Although I recognize that some published studies have used this approach, I suggest that this is not a standard

approach used, especially when attempting to characterize the tyramine sensitivity to a MAOI.

I emphasize that it is very uncommon and highly unusual (based upon published literature and proprietary data residing in the Agency) to require tyramine doses ≥ 800 mg to achieve a commonly applied tyramine pressor threshold/criterion (i.e. systolic blood pressure increment ≥ 30 mm Hg). Thus, it seems to me that the sponsor provided a misleading, unsatisfactory response to address this issue. In my experience of reviewing many publications assessing tyramine sensitivity, it is unusual and extremely uncommon to find many unselected subjects requiring tyramine doses of ≥ 800 mg to achieve a threshold response (i.e. systolic blood pressure increment ≥ 30 mm Hg) to tyramine administered under fasting conditions. **Based upon data derived from 84 unselected subjects (63 subjects under NDA 21479 for Zydys selegiline and 21 subjects from**

who had their tyramine sensitivity threshold defined in 105 baseline/pre-treatment tyramine challenge tests, none of these subjects require tyramine threshold doses > 700 mg. Thus, it is difficult for me to escape the conclusion that the sponsor's response in study P94159 is unusual. Correspondingly, as raised previously, these response raise the unanswered question that there may have be decreased potency with the sponsor's tyramine used in the fasting study and all 3 tyramine challenge studies involving tyramine addition to food and administration of tyramine added to food close to a meal. **The sponsor did not directly address the possibility that its tyramine used in all these studies may have had a decreased biological potency.**

End of Reviewer Comments

2 THE NUMBER OF SUBJECTS STUDIED IS SMALL, MAKING THE RESULTS LESS THAN RELIABLE

In Study P94159, a classical clinical pharmacology study, the number of subjects was indeed small but the conditions were quite stringent. This is also true for Study 132, where PD patients on rasagiline and LD received tyramine capsules before meal. The sensitivity is individual as each subject served as his own control. However, in the other 2 tyramine challenge studies, incorporated into the pivotal trials and conducted in the relevant PD population following 6 months of rasagiline treatment allowing for maximal inhibition of MAO to build-up, the number of patients is larger and the conditions are more relevant to reflect an extreme situation in a real life setting.

Classical clinical pharmacology studies with selegiline using similar design of comparison between oral tyramine doses needed to increase SBP at baseline and doses sufficient for the same effect after treatment (tyramine sensitivity factor .TSF), reported in the literature, indicate that the TSF calculated for selegiline is similar from one study to another, although in each study a small number of subjects was used. The sponsor summarized some data from

various studies in the literature investigating tyramine pressor responses. Barrett and colleagues summarized a series of studies with selegiline administered at different doses showing cross methodologies, that the TSF does not differ significantly. Although this study (P94159) was small, the TSF for selegiline was similar to values published in the literature, supporting the validity of the study and the reliability of its results.

It can be speculated that even if the number of subjects included in Study P94159 was higher, the results would not have been significantly different. It is evident from published studies that in spite of the variability of tyramine sensitivity in normal subjects, even a small number of subjects is sufficient to demonstrate a drug induced effect. However, in assessing the risk in PD patients especially those treated with LD, the classical clinical pharmacology approach was not the aim of the tyramine challenge studies. It was intended to assess if a relatively high to very high tyramine amount in food is capable to evoke a hypertensive crisis that would put the patients at risk while keeping their regular dietary habits. In fact, as mentioned above, this approach was supported by the agency. Originally, Dr. Temple suggested giving the patients a "provocative meal" containing high amounts of tyramine. Teva found this way to be less reliable than to add a fixed amount of tyramine to a low tyramine meal. We were concerned that if for some reason the patient did not like the given meal, he/she would not consume the target amount of tyramine. Therefore, tyramine in a capsule added into a light meal was chosen to allow standardization and to reduce variability of the amount of tyramine ingested between patients, but still reflect real life situation.

Reviewer Comments

- The sponsor notes that several published studies have included relatively small numbers of patients in a treatment group for investigating the effect of a MAOI on tyramine sensitivity. However, the sponsor did not recognize that the standard and amount of data for studying the effect of an MAOI drug on tyramine sensitivity may be quite different for an academic publication and a regulatory agency evaluating the tyramine sensitivity of a MAOI prior to approval. I agree that the extent of data often presented in a report published with an academic goal of contributing to the scientific literature can be based upon a relatively sparse/small number of subjects or a comparison of somewhat different populations or utilizing somewhat different approaches or study designs. The fact that many such publications exist in the literature should not necessarily be construed as an argument justifying that it is similarly acceptable that a regulatory agency should evaluate the effect of a MAOI on tyramine sensitivity and accept data that are not very robust because few subjects have been studied.

I believe that TSF data based upon results of a small number of subjects that are rather homogeneous (e.g. young healthy males) do not represent a very diverse population. These data provide mean point estimates for tyramine sensitivity (i.e. TSF) for 2 rasagiline doses. However, these point estimates may not provide a very accurate representation of the TSF experienced by a larger number of more heterogeneous subjects. Neither does this approach of focusing on results of small numbers of heterogeneous subjects permit the expression of any significant genetic diversity that may

occur when large unselected populations of patients are treated with a newly approved drug.

- The sponsor speculates that data (and implications of data) would be similar if larger numbers of subjects had been studied but I suggest that this is purely speculative. I further suggest that our regulatory assessment of this drug should be based upon actual data that is considered to be reasonable and relatively robust and not minimal or scanty for basing an important regulatory evaluation and assessment.
- I think that serious additional concerns about the reliability of the rasagiline TSF/TPR data are generated based upon the PK data collected in this study. 4 presents mean AUC_{0-1} and C_{max} for the healthy subjects challenged with tyramine under fasting conditions in Study P94159 after 1 or 2 mg daily rasagiline treatment. This table also compares these results with other mean AUC_{0-1} and C_{max} data derived from various doses studied in all phase 1 and/or phase 2 studies and normalized to 1 mg. The AUC for the 1 mg dose is not dose proportional to the 2 mg dose. Furthermore, the mean AUC for subjects treated with 1 mg rasagiline in this study is considerably lower (~ 40 %) than the AUC normalized to 1 mg based upon data from this study and all phase 1 and 2 studies collecting PK data. If the rasagiline exposure to 1 mg daily in these small number of subjects in this study is not representative of the possible rasagiline exposure that could be experienced after 1 mg daily rasagiline treatment of a large unselected population, then the tyramine responsiveness demonstrated in study P94159 and risk of hypertensive effects from tyramine ingestion during rasagiline treatment would also seem to be less than expected to occur after widespread, unselected marketing.
- The lack of dose-proportionality in this study and marked variability of AUC across formal PK studies investigating 1 mg daily rasagiline stimulated us to examine the raw PK data for this and other studies. Table 5 and Table 6 show individual subject results for plasma rasagiline for the 1 and 2 mg treatment groups respectively collected in the Paris fasting tyramine challenge study (P94159). Measurable plasma rasagiline levels (assay sensitivity 0.25 ng/ml) were typically found at only 3 sampling times (0.5, 1, 2 hours) after 1 mg treatment making it difficult to quantify AUC accurately. In contrast, rasagiline was measurable at all 5 sampling times after 2 mg treatment, suggesting why those data seem more reliable. In addition, the fact that the first sample was virtually always the highest value and that the individual PK curve was virtually always decreasing does not permit one to specify the true C_{max} when there is not an earlier lower value. **Results of other PK studies investigating 1 mg daily also exhibited the same problem of insufficient, measurable PK sampling to provide accurate PK results for AUC and C_{max} and other standard PK parameters. This discovery raises serious questions about the reliability of all important, PK studies (effect of renal impairment, hepatic impairment, gender, age) that are desired prior to approval. Consequently, the PK program desired at the time of approval seems to be inadequate for the effective doses (0.5 and 1 mg daily) that would be recommended in labeling.**

Table 4 Comparison of 1 and 2 mg Mean AUC and Cmax in Fasting Tyramine Challenge Study P94159 vs 1 mg Normalized Mean AUC and Cmax in All Phase 1 and 2 Studies

Study	Rasagiline Dose (mg)	Day	N	Mean AUC _{0-t} (SD)	Range AUC _{0-t}	Mean Cmax (SD)	Range Cmax
P94159	1 mg	9	6	5.8 (1)	4.4 – 6.9	7.5 (2.2)	
P94159	1 mg	10	6	5.5 (1.8)	3.5 – 7.6	5.8 (2.5)	
P94159	2 mg	9	9	24.7 (6.1)	16.4 – 34.4	12.1 (3.9)	
P94159	2 mg	10	10	23 (3.4)	18.5 – 28.1	10.9 (3.8)	
P94159	1 mg normalized	9	12	9.1 (4)	4.4 – 17.2	6.8 (2.1)	
P94159	1 mg normalized	10	12	8.5 (3.6)	3 – 14.1	5.6 (2.1)	
All Phase 1	1 mg normalized	Various	49	8.8 (3.5)	2.7 – 16.1	7.9 (2.9)	
All Phase 2	1 mg normalized	Various	48	9.5 (4.2)	1 – 23.8	5.6 (2.6)	
All Phase 1 and 2	1 mg normalized	Various	97	9.2 (3.9)	1 – 23.8	6.8 (3.0)	

Table 5 Plasma Rasagiline in Subjects Treated with 1 mg Daily Rasagiline on Day 10 (Steady State)

Study ref: P94159 Compound identif: PPAI								
Time(h)	LEMYA.01	KERTH.02	RAFTH.03	SIXCH.05	REIAU.06	JACAR.07	Mean	S.D.
0.0							0.00	0.00
0.5							5.43	3.15
1.0							2.51	1.04
2.0							0.90	0.37
4.0							0.11	0.18
8.0							0.00	0.00

BLQ : Below limit of quantification (0.25 ng.ml-1).

Table 6 Plasma Rasagiline in Subjects Treated with 2 mg Daily Rasagiline on Day 10 (Steady State)

Study ref: P94159 Compound identif: PPAI								
Time(h)	TRECE.10	BRAEM.12	PETRO.13	VAPAL.15	KLEOL.17	SEBPA.18	Mean	S.D.
0.0							0.00	0.00
0.5							8.30	5.76
1.0							8.48	2.41
2.0							4.51	1.37
4.0							1.60	0.40
8.0							0.48	0.13

BLQ : Below limit of quantification (0.25 ng.ml-1)

- The sponsor also points to various published data for selegiline and tyramine sensitivity based upon many different experimental designs and populations. However, I do not think that this referenced argument is very compelling, especially when none of the published studies (referred to) had evaluated tyramine sensitivity with selegiline based upon dosing as per the U.S. label (i.e. 5 mg BID).

End of Reviewer Comments

3 YOUNG HEALTHY VOLUNTEERS VS. ELDERLY PATIENTS - DIFFERENT TYRAMINE SENSITIVITY AND RASAGILINE PLASMA LEVELS

The agency is concerned that older men and women might not only be more sensitive to the effects of tyramine but also that they would have higher plasma levels of rasagiline. We did not find existing published data regarding the effect of age on tyramine sensitivity, as no study has compared blood pressure responses to tyramine in young and elderly individuals. It is known however, that in healthy unmedicated individuals there is no influence of gender and bodyweight. The sponsor referred to a study Psychopharm, 1978, 57 :33) suggesting that TSF responses to selegiline were similar in healthy volunteers and PD patients (Reviewer's comment : but did not mention that the Parkinson's Disease were not all elderly and that there were many differences in study design between the 2 groups making it impossible to make any meaningful comparison). Even if in the elderly the sensitivity to tyramine is increased, this sensitivity is normalized as the end point is a ratio between pre-treatment to post-treatment and not an absolute value. This ratio assesses the selectivity of rasagiline at the clinical relevant dose (1 mg/day). Indeed, in both Study P94159 and Study 132, subjects treated with 1 mg/day showed no increase in their sensitivity over that of placebo subjects. In view of the limited literature data available for age effect, we have re-analyzed rasagiline data to compare rasagiline plasma levels among young and elderly population as well as between men and women. For this purpose, data from phase I studies in young healthy volunteers were pooled and were compared with pooled data from phase I and II studies conducted in healthy subjects as well as PD patients. Some support could also be obtained from the population PK studies.

Reviewer Comments

- My comments related to the sponsor's response about Agency concerns increased tyramine sensitivity due to age or gender is provided below in subsections for age and gender.

End of Reviewer Comments

3.1 GENDER

We would like to address the agency's concern that only healthy males were enrolled in the Paris study. PK data derived from all clinical multiple dose studies, comparing females to males is presented for rasagiline in Table 1, Appendix 2. As discussed below, the data show that in both phase I studies using healthy subjects, and in phase II trials in PD patients, PK parameters (AUC 0-t, AUC 0-inf, Cmax and Tmax) of males are comparable to those of females at the relevant 1 mg clinical dose, and other dose levels and when dose is normalized to 1 mg dose. Therefore, based on the comparable pharmacokinetic profile, males in the tyramine interaction study are also representative of females. The mean exposure (AUC) of females in certain phase I studies was in the range of 7.7ng.h/mL (± 3.4), which is comparable to that of the males in the same studies (8.8 ± 3.5 ng.h/mL), for data normalized to 1 mg/d dose. Data in patients, both on rasagiline as monotherapy or in the add-on studies are demonstrating the same similarity between genders with female mean exposure of 12.9 ng.h/mL (± 6), which is comparable to that of the males in the same studies, 9.5 ng.h/mL (± 4.2), for data normalized to 1 mg dose. Combined male data from both healthy and PD patients show exposure of 9.2 ng.h/mL (± 3.9), which is comparable and therefore representative of the mean exposure of 11 ng/mL (± 5.8) in females in the same studies. Final supportive evidence for lack of gender effect in PD patients was demonstrated in both population PK studies, where gender had no effect on rasagiline clearance in early PD patients (TEMPO, Females n=57, Males n=93), or in patients on LD adjunct therapy (PRESTO, Females n=52, Males n=108). Regardless of the different PK sampling schemes across studies, health conditions, concomitant medication, age and other population differences, female PK parameters were comparable to those of males, either within or between studies. Both population PK studies failed to show a gender effect. Therefore data in males in the tyramine study are also valid for females.

Reviewer Comments

- The sponsor has provided a reference for the contention that there is no effect of gender on tyramine sensitivity in the unmedicated state. However, my concern about a suspected gender effect is not for the unmedicated state. My concern, based upon a suspicion of a PK difference manifested by increased exposure (e.g. AUC) of females vs males, is that females may exhibit greater sensitivity to tyramine for the same dose than that exhibited by males. In study 112 that compared PK data for a small number of male and female Parkinson's Disease patients at 3 different daily doses (0.5 mg, 1 mg, 2 mg), my attention was drawn to the fact that the mean AUC_{0-t} for all 3 doses was approximately 70 % greater for females than males.

Of interest, , the sponsor's table showed that the AUC for the 2 mg dose in females was 26 (vs 19 for males) but the original NDA submission had shown that AUC for the 2 mg group was 36. When queried about this discrepancy, the sponsor noted that data from one subject (# 578) who had a very high AUC (47) had been omitted because one sample was very high. When this patient's value was included again, the sponsor confirmed that the mean AUC was 36 (nearly 2 fold the mean value of the males at 2 mg). It is also relevant to note that subsequent to our discovery of the inadequate PK sampling for estimating PK parameters (especially AUC and Cmax) in study P94159, I found out that sampling in this study (112) only occurred at 0.5, 2 and 4 hours. Plasma rasagiline was measurable

at all 3 times in each group of patients and typically, the 0.5 hour sample was the highest value. As mentioned earlier, given these limitations, it would not be possible to calculate C_{max} in this study accurately because of inadequate sampling and lack of a lower value rasagiline level prior to the highest level at 0.5 hours (1.5 hours prior to the next sampling time at 2 hours after dosing).

- Study 231 may also bear some relevance to the consideration of gender differences for PK between females and males for plasma rasagiline. A relatively small number of males and females (n = 4-10 per dose and gender group) Parkinson's Disease patients underwent PK sampling at 0.5, 2 and 4 hours after rasagiline 1, 2, or 4 mg daily. Although the female mean AUC was only 12 % greater than males for the 1 mg dose group, both the 2 and 4 mg dosing groups showed that mean female AUC was ~ 30 % greater than that of mean male AUC.
- Although there were some studies (6) in which males and females evaluated in the same study could be compared for possible PK differences. I asked the Biopharmaceutical reviewer (Dr. Andre Jackson) to comment on the reliability of the PK data in these studies for comparing AUC and C_{max}. With the exception of 3 PK studies (424, 425, and 430), Dr. Jackson informed me that he considered data from the other 3 studies to be of "questionable value" for reliability of the PK data. However, I note that studies 424 and 425 were PK studies evaluating the effect of impaired hepatic and renal function respectively on rasagiline (1 mg/day) and the data from these studies included only small numbers (study 424 – 3 females vs 5 males; study 425 – 2 females vs 6 males) of subjects. Study 430 studied the interacting effect of theophylline with rasagiline and contained somewhat larger numbers of subjects (11 females vs 7 males). This latter study (consisting of larger numbers of subjects than studies 424 and 425 but still less than desirable) showed a mean 27 % greater rasagiline AUC_{0-t} for females compared to males.
- **In general, I consider interpreting pooled PK data across studies as potentially problematic and that this approach is not very accurate for confirming nor refuting a PK difference.** Looking at results from the 3 PK studies (assessing the PK effect of a 1 mg daily dose) clearly emphasizes this point. There were marked differences in mean AUC_{0-t} for the same gender when you compared the lowest and highest mean results among the 3 studies. These results showed AUC_{0-t} of 9.5 vs 3.1 for the highest and lowest female means (a 3 fold difference). These results showed AUC_{0-t} of 7.5 vs 3.5 for the highest and lowest male means (a 2 fold difference).
- Based upon the sponsor's pooled analyses across studies, the mean AUC_{0-t} for females was 36 % greater than that of males in all phase 2 studies (normalized to 1 mg daily dose) and was 19 % higher for females than that of males for all phase 1 and 2 studies (normalized to 1 mg daily dose).
- In summary, there are serious PK limitations due to the insufficient number and time of plasma PK sampling in studies collecting PK data after 0.5 and/or 1 mg daily rasagiline

treatment in healthy volunteers or patients. Thus, I do not think that there are reliable PK data (particularly for AUC and C_{max}) that confirm nor refute that rasagiline exposure is increased in females vs males. Such data would ideally come from a formal PK study comparing significant numbers of healthy males and females in the same study. In the absence of robust or compelling PK data to the contrary showing that there is no significant increase in exposure in females, I think that mild – modest increased exposure should be considered in females until there are reliable data to refute this suggestion derived from what I would characterize as preliminary data.

- **The suggestion of increased exposure in females is not necessarily dramatic (e.g. several fold difference) in isolation. However, I suggest that a modest mean increase of 30-50 % could be worthy of consideration given the possibility that this difference could be associated with other factors (age, concomitant LD, hepatic impairment, concomitant treatment with metabolic inhibitor of CYP1A2) increasing exposure. The net additive effect of these several factors could potentially result in a several fold increased exposure (compared to subjects without these factors increasing exposure) for a certain dose such as 1 mg daily. For example, a subject with these combined factors resulting in a cumulative 300 % increased exposure might experience an AUC similar to an AUC of subjects treated with 4 mg. Given the facts that : 1) we already have a suspicion that there is increased tyramine sensitivity to 2 mg daily rasagiline; 2) the extent of this increased tyramine sensitivity is not precisely quantified; and 3) we have no idea of the extent of the risk of increased tyramine sensitivity for a normal healthy subject treated with 3 or 4 mg daily, this unsettled issue is an important one that should be resolved prior to approval of rasagiline.**
- Dr. Jackson, the Biopharmaceutical reviewer for rasagiline, agrees with my perspective and thinks that there is a possibility that there is increased rasagiline exposure in female subjects. However, there is as an important caveat to consider. **Based upon the preliminary PK data at hand, Dr. Jackson thinks that the PK data for ≤ 1 mg rasagiline treatment are not clearly reliable and that the available data do not allow us the opportunity of assessing the effects of many important factors/variables on rasagiline PK in addition to gender.**
- Our approvable letter also requested a formal evaluation of the effect of LD on rasagiline clearance (“You need to formally evaluate the effect of levodopa on rasagiline clearance.”) . This request had been made relative to the possibility that LD could have a PK drug-interaction on rasagiline that could increase exposure and consequently, increase tyramine sensitivity risk.

The sponsor’s response to this request was : “Teva accepts the current FDA proposed labeling on the effect of levodopa on rasagiline clearance, which

I consider this response to be a useless one because it does not directly address our request. The sponsor has not chosen to conduct a drug-drug interaction study assessing the effect of LD on rasagiline PK nor responded by discussing why the data related to these conflicting study results are more believable/reliable for the study showing no effect of LD on rasagiline exposure.

Previously, the sponsor had conducted a PK drug-drug interaction study assessing the effect of rasagiline on plasma LD, but unfortunately, the sponsor did not assess in this same study the effect of LD on rasagiline. I think that the best way to address this issue is by conducting a formal PK drug-drug interaction study assessing the effect of LD on rasagiline PK.

End of Reviewer Comments

3.2 AGE

The Agency is concerned that older men and women might have higher plasma levels of rasagiline than younger patients.

It can be demonstrated that pharmacokinetic parameters in older subjects or Parkinson's Disease patients are comparable to those of young subjects based on data derived from all clinical multiple dose studies, comparing young (range of 19-41.5 years) to older subjects (range 41.6-76 years) (Table 2 in Appendix 2 = summary table compiling PK data in subjects of various ages in different studies). As discussed below, the data show that both a comparison between the two age cohorts in phase I healthy subjects, as well as a comparison across phase I and phase II trials in PD patients, show similar PK parameters (AUC 0-t, AUC 0-inf, C_{max} and T_{max}) at the relevant 1 mg clinical dose, and at the other dose- normalized levels in these two cohorts. Therefore the young subjects used in the tyramine study (P94159) are representative of the whole population treated with rasagiline including elderly.

The mean exposure of older subjects in Studies 1012/424, 1012/425 and sub-cohort of ages >40 years in Study 1012/430 (phase I studies where older subjects, range 41.5-62.7 years, were included) was of 6.2 ±3.2 ng.h/mL. This is comparable, and even lower than the mean exposure of 10.2±2.7 ng.h/mL of the younger subjects in the same studies, (data normalized to 1 mg dose).

PK data from the phase II trials (TVP-1012 = rasagiline) in patients, (TVP-1012/231, TVP-1012/112 and TVP-1012/132) is obtained from older subjects (range 42.6-76 years), and the mean exposure (10.8 ±5.2 ng.h/mL) was comparable to the values in young healthy subjects in the tyramine study (9.1 ±4 ng.h/mL for data normalized to 1 mg dose. Combined analysis of PK parameters in older healthy or PD patients in all the above-mentioned trials show a mean exposure of 9.6 ±5.2 ng.h/mL which is also comparable to the young subjects in the tyramine study (P94159), and to the range observed in all phase I studies in young subjects.

A minimal negative effect of age on rasagiline clearance was found in early Parkinson's Disease patients (TEMPO, Median age 62, range 32-79 years). An illustration of the low significance of

the latter is that quantitatively, only 11% decrease in clearance is predicted between the ages of 60 to 79 years. Evidence for lack of age effect on rasagiline clearance in PD patients on levodopa adjunct therapy was demonstrated in the PRESTO population PK study (median age 63 range 32-79 years).

Thus, a comparison based on differentiation between younger subjects (as in the tyramine study), and older subjects (aged above 40 years old), shows that regardless of differences in subjects characteristics, older subjects had similar exposure parameters to those of younger healthy subjects.

Population PK studies failed to show a clinically significant age effect Therefore data in young subjects in the tyramine study is also valid for older subjects.

Reviewer Comments

- It is well known that there may be substantial PK/PD differences for different drugs for various outcome measures between the elderly (e.g. ≥ 65 years old) subjects and non-elderly (< 65 years old) subjects. However, I am not aware that there are any data that show that the tyramine sensitivity based upon PD differences (despite similar PK exposures) is greater or lesser in elderly subjects compared to non-elderly subjects. I do not think that this issue has ever been investigated. Furthermore, the possibility exists that elderly patients could exhibit increased sensitivity to tyramine after rasagiline treatment based upon PK differences (vs non-elderly) such that exposure (e.g. AUC) was increased. Population PK data do suggest that there is an age-related increase (~ 1 %/year) in rasagiline exposure. Thus, it is conceivable that elderly patients could experience an increase in exposure of perhaps 30-50 % and this increase, coupled with other factors causing an exposure increase (e.g. female gender, hepatic impairment, CYP1A2 inhibitor, etc. or any combination of these factors) could result in substantially increased rasagiline exposure and consequently increased tyramine sensitivity and potentially increased risk for a “cheese” reaction. Significant hypertensive reactions due to tyramine ingestion would be especially unwanted in the elderly who already usually have increased risks for myocardial infarction and stroke.
- There were no formal PK studies of rasagiline in elderly vs non-elderly subjects. The sponsor provided a table (Table 1 in Appendix 2) of studies in which PK data were collected and categorized these studies as investigating “young” or “elderly” subjects but the sponsor did not define “young” nor “elderly.” This table showed the number and mean age and age range of healthy or Parkinson's Disease subjects along with rasagiline dose/treatment duration and mean PK parameters (AUC_{0-1} , AUC_{0-inf} , C_{max} , T_{max}) and ranges of these parameters. Interestingly, the sponsor categorized studies as “elderly” when the lowest age of subjects was ≥ 41 years of age! In these categorizations when the age range exceeded 65 or older, it was not possible to have any idea how many subjects would actually be classified as “elderly” using the Agency’s regulatory definition of ≥ 65 years old (e.g. the age cut-off used to describe geriatric labeling and usually used for

subgroup efficacy analyses). None of these individual studies showed a comparison of data for subjects ≥ 65 years old vs ≤ 65 years old.

- In my view, the sponsor's summary table and analyses did not facilitate any serious assessment of this potential age issue for increased PK exposure in elderly patients. I requested that the sponsor conduct and submit additional analyses including showing pooled PK data for different age windows from young ages through elderly subjects. In addition, a specific pooled analysis of AUC_{0-t} was requested using a cut-off of ≥ 65 years old and < 65 years old. The pooled analyses of data across studies for AUC_{0-t} did not suggest a clear difference in AUC from young to old age windows (18-24, 25-34, 35-44, 45-54, 55-64, 65-74). Although the pooled analysis of AUC_{0-t} across several studies using the 65 year old cut-off did not suggest any difference for elderly compared to non-elderly subjects, there were relatively few subjects ($N = 17$) in the elderly category compared to a much larger number ($N = 110$) in the non-elderly group. Thus, I consider the question of an effect of age on rasagiline exposure, particularly for elderly subjects ≥ 65 years old, as still unresolved. In the absence of robust or compelling PK data to the contrary showing that there is no significant increase in exposure with age, I think that mild – modest increased effect should be considered. A formal PK study comparing elderly and non-elderly males and females in the same study is highly desirable to confirm or refute the suggestions of increased rasagiline exposure based upon gender and age.
- I point out that the non-robust TSF data accumulated from small numbers of healthy Study P94159 per treatment group were based upon young subjects aged 19-32 years. In the absence of robust or compelling PK data to the contrary showing that there is no significant increase in exposure in elderly vs non-elderly subjects, I think that mild – modest increased exposure should be considered in elderly subjects.
- Dr. Jackson, the Biopharmaceutical reviewer for rasagiline, agrees with my perspective and thinks that there is a possibility that there is increased rasagiline exposure in elderly subjects.

End of Reviewer Comments

4 BP CRITERIA : 3 CONSECUTIVE MEASUREMENTS VS. ONE SINGLE MEASUREMENT

The agency pointed out that in Study P94159 only one SBP elevation was considered necessary to reach the BP criterion whereas in other studies, 3 consecutive elevations were considered obligatory. Indeed, per protocol, only one elevation in BP was considered as necessary to reach the BP criterion, and this is far more stringent than what is acceptable and at the same time not a good enough criterion (as it can also represent a sporadic, non significant one-point elevation). Therefore the clinical criteria were also taken into account for definition of the endpoint, meaning that it was in the discretion of the physician to decide if the subject had met the end-point of responsiveness even if he had not reached the 30 mmHg increase in BP.

In 3 cases where TYR30 per protocol was not formally met, clinical signs and symptoms supported a conclusion of responsiveness to tyramine. These clinical criteria were more conservative than the per protocol criteria. As stated above, the reason that the BP criterion was not regularly met is the fact that the subjects were not pre-screened. It is relevant to mention that the site in Paris where the study was conducted was inspected by the FDA auditor on 3-7 May, 2004 with satisfying conclusions.

Reviewer Comments

- I agree that the requirement of allowing a single systolic blood pressure increment (the requirement for determining a tyramine-induced increment in study P94159) to define the TYR30 threshold increases the risk of false, positive, spurious increments that do not necessarily reflect a true tyramine-induced increment. In contrast, requiring 3 consecutive increments of ≥ 30 mm Hg at close intervals (e.g. 5 minutes) would increase the likelihood that the threshold increase was real and related to tyramine rather than a potentially spurious increments unrelated to tyramine. A study design requiring 2 or 3 consecutive threshold blood pressure increments is an approach that has been used in by some investigators to ensure the likelihood of determining true tyramine-induced increments. I strongly concur with this approach. Of interest, the sponsor seemed to appreciate this possibility and this approach because the 3 tyramine challenge studies in which tyramine added to food and given near a meal required 3 consecutive threshold systolic blood pressure increments to define a threshold increment resulting from tyramine challenge. Considering the fact that I consider study P94159 to be the most important of the tyramine challenge studies, it is disconcerting that this study could have determined tyramine threshold doses (and TSFs) that may have been spurious because the characterization of the pressor threshold was based upon a single measurement that could have represented a false positive.
- I consider the use of “clinical criteria” for characterizing the tyramine threshold dose to be useless exercise because this application of “clinical criteria” was not scientific and objective according to any pre-specified approach. This use of “clinical criteria” dose appeared to be an ad hoc, subjective approach devised and applied by the investigator.
- I find it extremely interesting that the sponsor refers to “satisfying conclusions” regarding the DSI inspection of the Paris study P94159 when 2 conclusions from the DSI monitor notes questions about the reliability of the conduct of this study. Based upon other comments noted in the DSI inspection summary report communicated to the DNDP, I think that these conclusions are reasonable. I do not think that the sponsor ever saw the conclusions shown below for the fasting tyramine study conducted in Paris. In particular, I emphasize that the 2 DSI conclusions markedly contrast with the impression of the sponsor about this inspection.

The following conclusions shown in italics are the quoted conclusions of the FDA/DSI inspection for the Paris site for Study P94159 :

1. "The site lacked documentation of the actual foods consumed by the subjects during study participation. Furthermore, while the site claimed that protocol requirements regarding fasting conditions were met, the CRF was the only document provided to support this claim. As described above (item 1), the CRF did not record the actual time when fasting started and ended. In light of these findings, there is no written assurance that fasting or dietary restrictions were met."
2. "There is no assurance that blood pressures were taken at the times defined by the protocol in that the site failed to document the actual times of manual measurements, and did not verify that automated measurements conformed to the protocol defined times (item 3 above). The medical officer should evaluate whether the unscheduled, minute by minute blood pressure measurements may have biased the outcomes."

End of Reviewer Comments

5 TYRAMINE PLASMA LEVELS AND MAO-A INHIBITION

The agency noted that the tyramine levels which were measured in subjects participating in Study P94159 were increased even for the 1 mg/day dose level and that this could be a sign for some degree of inhibition of MAO-A.

Tyramine plasma levels were measured in this study for 2 reasons: (1) to show that there was a systemic exposure and (2) due to the complicated structure of this study (where on Days 9 and 10 tyramine was administered twice), it was important to find out whether tyramine was still detected in the plasma prior to the second administration. For this purpose, plasma samples were taken at pre tyramine dose and at 1 hr after each tyramine administration.

In this section, the sponsor repeated arguments about the lack of significance of measuring minor changes in low plasma tyramine levels after rasagiline treatment and the lack of a reduction in plasma DHPG after rasagiline treatment as suggesting no significant MAO-A inhibition. The sponsor referred to similar publications supporting its arguments as were presented and discussed in Part 2 (1.5 TYRAMINE PLASMA LEVELS DHPG AND MAO-A INHIBITION).

The sponsor commented that the proportion of subjects, in the 1 mg/day dose, in whom tyramine plasma levels above 5 ng/ml were measured at the low tyramine doses (50 and 100 mg) is small. This finding indicates that at relevant tyramine doses (even under fasting conditions), the ability of intestinal and liver MAO-A to metabolize the tyramine was not compromised.

In addition, correlation (Pearson correlation) between the plasma concentration of tyramine (as measured 1 hour after tyramine administration) and the SBP values (from tyramine administration and 3.5 hrs thereafter, in 5-minute intervals) was tested using the following 3 approaches (with respect to the calculation of SBP) :

- The AUC (Area Under the Curve) was calculated for systolic blood pressure (calculation was done for each tyramine dose administered).
- Mean of systolic blood pressure was calculated for each tyramine dose.
- The maximum systolic blood pressure was calculated for each tyramine dose.

The Pearson correlation was calculated for each method against the tyramine concentration determined in the plasma. The sponsor said that there was no evidence for correlation between tyramine dose and SBP exists at any of the approaches taken.

The sponsor suggested that the significance of some changes in low plasma tyramine levels is uncertain taking into account the great intra-subject variability and the inconsistency of tyramine plasma levels across treatment groups. The sponsor further suggested that inhibition of intraneuronal MAO is probably much more significant in the tyramine pressor response and not the actual plasma tyramine level. Sole increase in tyramine levels may reflect the change in the intestinal tyramine metabolism and absorption rather than inhibition of intraneuronal MAO-A.

Reviewer Comments

- I agree with the sponsor's arguments and discussion outlined above that seems reasonable. I concur that the data showing some increments in plasma tyramine levels after rasagiline treatment were not necessarily compelling data indicating a significant extent of MAO-A inhibition within neuronal synapses that would be required to facilitate a hypertensive "cheese" reaction.

End of Reviewer Comments

6 TYRAMINE BIOAVAILABILITY AND FOOD

The agency is concerned that the way tyramine was administered (with applesauce or with a light meal) might cause a reduction in the bioavailability of tyramine and therefore, failure to show elevations in BP could be "false negative."

There were 2 types of tyramine challenge studies in the rasagiline clinical program, those which were under fasting conditions and those which tried to reflect real life conditions by administering tyramine near or with a meal and possibly with applesauce, yogurt, frozen yogurt, or ice cream. In this section, the sponsor repeated arguments about the effect of food on tyramine bioavailability in general and in its specific studies and also referred to similar publications supporting its arguments as were presented and discussed in Part 2 (3. TYRAMINE BIOAVAILABILITY AND FOOD).

In addition, the sponsor referred to data showing that administration of 3 other drugs (lansoprazole 30 mg either as intact gelatin capsules or enteric-coated granules from opened capsules in one tablespoon of applesauce; contents of Adderall XR capsules into applesauce; — - anhydrous theophylline in the form of long-acting beads within a dye-free hard gelatin capsule) with applesauce did not alter bioavailability of these 3 other drugs. The sponsor concluded that because applesauce did not alter the bioavailability of these other 3 drugs that applesauce per se does not affect bioavailability including that of tyramine and is similar to tyramine given as an intact capsule under fasting conditions. The sponsor further noted that the only thing that interferes with the bioavailability of tyramine is food, where a high fat/protein meal shows a more pronounced effect than a standard meal.

Reviewer Comments

- I have described my main concerns regarding the issue of how food can affect tyramine bioavailability and complicate the sponsor's tyramine challenge studies earlier in my review. My major concerns have been outlined in my respective comments in Part 1 (see sponsor's expert consultant assessments under section : Tyramine bioavailability in food and Tyramine challenges in studies 132, 232 and 133) and in Part 2 (section : Tyramine bioavailability in food). I have not repeated my comments and concerns again here.

My original clinical review of NDA 21641 also presented and discussed in detail my various concerns (and relevant scientific publications) about the validity of the sponsor's studies (132, 232, 133) in which tyramine was administered near or with a meal and by adding tyramine to food (applesauce, yogurt, frozen yogurt , or ice cream). I refer the reader also to my Clinical Review (entered 6/29/04; signed 7/1/04) of the original submission of this NDA.

End of Reviewer Comments

7 PATIENTS EXHIBITING PRESSOR RESPONSE

The sponsor repeated a similar response as it presented in Part 2 (4. PATIENTS EXHIBITING PRESSOR RESPONSE).

Reviewer Comments

- I have provided my interpretations of the data for patients exhibiting pressor responses to tyramine challenge earlier in Part 1 (see sponsor's expert consultant responses/assessments under section : Tyramine challenges in studies.132, 232 and 133) and in Part 2 (section 4 Patients Exhibiting Pressor Response). I have not repeated my comments and concerns again here.

End of Reviewer Comments

8 EXPOSURE TO UNRESTRICTED DIET, AE PROFILE AND BP

The Agency Approvable Letter did not specifically comment on the rasagiline exposure relative to unrestricted tyramine diet and adverse event profile relative to blood pressure. However, the letter did note that if the sponsor did not want to conduct the recommended tyramine study, then the product labeling would need to require that patients restrict the diet with regard to tyramine containing products. In this section, the sponsor presented similar responses in Part 1 (Self-monitoring of the Blood Pressure in the PRESTO Trial and Cardiovascular Events During the Development of Rasagiline) and in Part 2 (2.1 HOME BP MEASUREMENTS BEFORE AND AFTER MEALS and 2.2 EXPOSURE TO UNRESTRICTED DIET AND AE PROFILE). I have not repeated my comments and concerns again here.

Reviewer Comments

- I have described my main thoughts and concerns regarding the adverse event profile of exposure and blood pressure measurements, particularly while on an unrestricted tyramine diet. My thoughts and concerns have been outlined in my respective comments in Part 1 (expert consultants views in sections : Self-monitoring of the Blood Pressure in the PRESTO Trial and Cardiovascular Events During the Development of Rasagiline) and in Part 2 (2.1 HOME BP MEASUREMENTS BEFORE AND AFTER MEALS and 2.2 EXPOSURE TO UNRESTRICTED DIET AND AE PROFILE).

End of Reviewer Comments

9 REGULATORY INPUT RECEIVED FROM FDA DURING THE IND

The Agency Approvable Letter did not specifically comment on Regulatory Input provided to the sponsor during the IND. However, the sponsor commented on some regulatory input received during the IND stage.

During the IND stage Teva received close input and guidance from the Agency on the clinical development of rasagiline and in particular on issues related to potential rasagiline/tyramine interaction. The potential rasagiline/tyramine interaction has been brought up and discussed with the FDA at the end of phase II meeting held on June 1997, and at a meeting with the Division held on August 2000, followed by a teleconference a few days later.

The clinical trial report of the tyramine interaction clinical pharmacology study in healthy volunteers P94159 was submitted to the Agency under the IND (as part of the pre-meeting package dated 18 April, 2000).

At the meeting between Teva representatives and FDA on August 17, 2000 (and the teleconference meeting of August 23, 2000) the protocol TVP-1012/133 (PRESTO) and the need for tyramine restriction in this study were discussed. FDA expressed no concerns as to the

selectivity of 1 mg/day rasagiline as assessed by Study P94159 which was discussed in the meeting. No specific comments on this study were received.

The official meeting minutes (as submitted in the NDA) include the following statements.

“Introductory FDA Comments :

There are no affirmative, formal data to indicate that 1 mg/day of rasagiline \pm LD may be associated with a tyramine interaction. The evaluation of any potential for tyramine interaction risk with 1 mg/day rasagiline should be done in a placebo-controlled study with no tyramine restriction.”

Although the FDA was aware of the tyramine interaction study (P94159) and its outcomes, it agreed to Teva's development plan to evaluate any potential tyramine interaction risk at the end of a 6- month placebo-controlled study (PRESTO). The concept of a long-term, real-life tyramine sub-study was also agreed upon in the end of phase II meeting which was held on June 18, 1997 (meeting minutes in the application). Dr Temple was in favor of a “provocative meal” at the end of study treatment with rasagiline.

In addition, the completed development program was presented during the pre-NDA meeting and no lack of any clinical pharmacology study was indicated by the Division.

Reviewer Comments

- I do not believe that the sponsor provided detailed results of the Paris study (P94159) at the time that results of this study were discussed with the DNDP. Because a detailed review of these data by DNDP was not possible at the time of meeting with DNDP, it was not possible for the many shortcomings that I have identified in this study to have been raised, addressed, and discussed.
- I do not believe that any potential concerns were raised by either the sponsor nor DNDP relative to conducting an assessment of tyramine sensitivity by exposing subjects to tyramine with food. I am not aware that the discussion of these issues with the DNDP raised the concern that assessing tyramine sensitivity by adding tyramine to food and/or near a meal could be problematic because of decreased bioavailability of tyramine associated with this approach.
- It should be noted that Dr. Temple had recommended assessing tyramine sensitivity associated with rasagiline treatment by exposing subjects to a provocative meal containing tyramine. However, the sponsor chose a different approach and added tyramine to food and/or administered tyramine near a meal without documenting how tyramine bioavailability might be altered relative to AUC, C_{max}, T_{max} and time to maximal blood pressure response. I am not certain if there was much discussion of this approach, potential problems with this approach, and the potential need for validating this

approach. Furthermore, neither am I aware that much data exist indicating how reproducible or robust blood pressure responses are by provoking blood pressure responses to tyramine in food and/or drink containing certain amounts of tyramine after treatment with a drug that inhibits MAO-A and increases sensitivity to tyramine.)

End of Reviewer Comments

The following sponsor conclusions for responses described in this section are presented in italics as direct quotes.

“10 CONCLUSIONS

- *Rasagiline maintains its selectivity toward MAO-B after long term exposure.*
- *Rasagiline 1 mg/d (the clinical dose) is more selective than selegiline at the clinical dose of 10 mg/d. Rasagiline at two fold higher dose than the clinical is comparable to the clinical dose of selegiline.*
- *Selegiline at 10 mg/d has no tyramine restrictions accordingly there should be no tyramine restrictions for rasagiline clinical dose as it has a higher safety ratio.*
- *There were no tyramine-related adverse events during the pivotal clinical studies with rasagiline although the patients in these studies did not restrict their diet.*
- *Cardiovascular adverse events such as MI, CVA and TIA were evenly distributed between treatment groups.*
- *In the population of PD patients blood pressure variability is common as can be seen from ambulatory home measurements.*
- *The episodes of increase in blood pressure are equally distributed between treatment groups and occur frequently in placebo patients not treated with rasagiline and irrespective of the meal content.*
- *Tyramine pressor effect seen in challenge studies under the most extreme conditions (occurred only with dose two times higher than the clinical dose) should be viewed in perspective of absolute potential sensitivity and should not imply real life risk.*
- *No events that signal concern were observed with rasagiline 1 mg. Moreover the profile of the 1 mg dose was identical to that of the placebo indicating no increases sensitivity to tyramine with the clinical dose of rasagiline.*
- *Therefore, the Sponsor believes that the administration of rasagiline 1 mg/day with and without levodopa is safe in PD patients and does not require tyramine restricted diet.”*

Reviewer Comments

- I differ with many of the sponsor's conclusions outlined here and will provide my view of each of the sponsor's 10 conclusions.
- I cannot necessarily conclude that rasagiline maintains its selectivity toward MAO-B after long term exposure because I think that rasagiline's selectivity toward MAO-B has not been adequately characterized.
- I cannot necessarily conclude that that rasagiline 1 mg/d (the clinical dose) is more selective than selegiline at the clinical dose of 10 mg/d because I think that rasagiline's selectivity toward MAO-B has not been adequately characterized . The preliminary results of Study P94159 suggest that there may less sensitivity to tyramine for 1 mg rasagiline daily compared to selegiline dosed as 10 mg QD (i.e. more selectivity for MAO-B). However, I think that it is premature to draw this conclusion based upon the many concerns with this study and especially the small number of homogeneous subjects (young males) per treatment group.
- I cannot necessarily conclude at this time that rasagiline treatment at ≤ 1 mg daily should not have dietary tyramine restrictions because the sponsor thinks that rasagiline has a higher safety ratio than selegiline (10 mg daily) and because selegiline does not have a dietary tyramine restriction. Selegiline was approved (1989) many years ago without any tyramine sensitivity studies. Selegiline was approved without dietary tyramine restrictions based upon the analyses of cardiovascular adverse events and hypertensive "cheese" reactions in the NDA safety experience. Relatively recent data by the sponsor of selegiline has suggested that it (10 mg daily) has a TSF of ~ 2 but data from some other sources (although not necessarily very precise nor reliable) have suggested that the TSF for 10 mg daily may be somewhat > 2 . The standard for the basis of an MAO-B inhibitor in 1989 is substantially different now that it was then. Preliminary TSF data from a small number of homogenous subjects (young health males) suggests that rasagiline at 1 mg daily can have a lower tyramine sensitivity risk than that of selegiline at 10 mg daily. However, I consider these data to be preliminary, not very robust, and not yet sufficient to characterize the tyramine sensitivity risk adequately for rasagiline. Whether any dose of rasagiline requires dietary tyramine restriction should be suggested by adequate data characterizing the risk for tyramine sensitivity.
- I agree with the sponsor that there were no clear adverse effects in the pivotal clinical trials (for patients without dietary tyramine restriction) that suggested a relationship to tyramine exposure. However, the total number of patients is relatively limited compared to the exposure that would likely occur after an approval. In addition, nearly 40 % of the safety experience occurred on tyramine dietary restriction. It is possible that a significant frequency of adverse tyramine reactions could possibly occur with approval despite that fact that they were not observed in the limited safety experience of the NDA.

- I agree that cardiovascular adverse events such as CVA and TIA were evenly distributed between treatment groups. However, the frequency of MIs was ~ 4 fold greater associated with rasagiline vs placebo/entacapone. Dr. Lisa Jones has addressed this issue in her Safety review.
- I agree with the sponsor that blood pressure variability is relatively common in Parkinson's Disease patients as can be seen from ambulatory home measurements. However, I have noted the limitations and my reservations regarding the home blood pressure monitoring data earlier in the respective sections (Part 1 - expert consultants views in sections : Self-monitoring of the Blood Pressure in the PRESTO Trial and Cardiovascular Events During the Development of Rasagiline) and Part 2 – section 2.1 HOME BP MEASUREMENTS BEFORE AND AFTER MEALS and section 2.2 EXPOSURE TO UNRESTRICTED DIET AND AE PROFILE) dealing home blood pressure monitoring.
- I agree with the sponsor that based upon its analyses of the PDC for certain threshold blood pressure events that the episodes of increase in blood pressure seem equally distributed between treatment groups and occur frequently in placebo patients not treated with rasagiline and irrespective of the meal content. However, my requested analyses of the treatment difference (i.e. change from baseline = treatment - baseline) for the rate and incidence of hypertensive outliers (Table 2, Table 3) and treatment effect (rasagiline – placebo) raise some questions about hypertensive effects of rasagiline based upon the home blood pressure monitoring. In addition, I have noted earlier my various reservations and concerns about how robust and informative these data. The sponsor's analyses excluded much blood pressure data and in particular the study design did not permit much blood pressure data to be collected at a later time after a meal (e.g. > 150 minutes, at times when most peak pressor responses are occurring to tyramine added to a meal). Thus, these data may not have been collected in a most sensitive fashion for characterizing significant meal –related blood pressure increments. I also note that there are no substantial home blood pressure monitoring data for the 2 mg daily rasagiline treatment and that the available data are only for \leq 1 mg daily.
- I disagree with the sponsor's conclusion that the tyramine challenge studies were conducted under the most extreme conditions to capture tyramine-induced blood pressure increments because the sponsor did not validate that its approach of adding tyramine to food and administering this challenge near a meal was very sensitive for detecting a significant tyramine pressor response. Perhaps, the most extreme tyramine challenge study is assessing the effect of rasagiline during fasting in a well designed study that overcomes the limitations of the previous fasting tyramine study (P94159).
- Although I agree with the sponsor that no signal (e.g. no increased TSF) was shown in the fasting tyramine study for 1 mg daily rasagiline vs placebo, I think that these data are not very robust and thus view them as preliminary because I do not consider that the tyramine risk was adequately characterized. A major concern with the potential reliability

of the accuracy of these data relates to the fact that these data are based upon studying small numbers of a homogeneous healthy population (young males). Neither did the sponsor adequately address Agency concerns that there may have been decreased biological potency of the tyramine used for challenge in all the studies (same tyramine source was used for all studies). In the fasting study, a very large percentage (67 % - 18/27) of subjects required a very high tyramine threshold dose (800 mg) or did not exhibit a TYR30 at doses up to 800 mg. This experience is a marked outlier from my review of the literature and FDA data (105 tyramine challenge tests in 84 subjects exhibited a TYR30 threshold at ≤ 700 mg tyramine). Furthermore, the DSI inspection conclusions raised suspicions about the reliability of the study conduct at the site relative to following dietary requisites and documenting appropriate blood pressure monitoring.

- I disagree that administration of rasagiline at 1 mg daily is safe and does not require tyramine restriction because of my many concerns previously outlined describing the inadequacies of the sponsor's tyramine challenge data and the need to collect reliable robust data from a substantial number of older males and females.

End of Reviewer Comments

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/s/

Leonard Kapcala
7/28/05 11:32:15 AM
MEDICAL OFFICER

John, Here is my review of the response to
approvable letter for rasagiline and the tyramine sensitivity
issue. Please contact me if anyu questions. Thanx.
Len

John Feeney
8/1/05 12:19:06 PM
MEDICAL OFFICER
See my cover memo