

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-641

APPROVAL LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-641

TEVA Pharmaceuticals LTD
Attention: J. Michael Nicholas, Ph.D.
Senior Director, U. S. Regulatory Affairs and Pharmacovigilance
425 Privet Road, P.O. Box 1005
Horsham, PA 19044-8005

Dear Dr. Nicholas:

Please refer to your new drug application (NDA) dated and received September 5, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azilect (rasagiline mesylate) 0.5mg and 1 mg Tablet

We acknowledge receipt of your submissions dated:

19-Jul-2005	4-Aug-2005	11-Aug-2005	12-Aug-2005
08-Nov-2005	20-Jan-2006	09-Feb-2006	17-Mar-2006
27-Mar-2006			

The March 17, 2006 submission constituted a complete response to our August 4, 2005 action letter.

This new drug application provides for the use of Azilect (rasagiline mesylate) in the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-641.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated March 17, 2006. These commitments are listed below.

1. A formal tyramine challenge study in the fasted state. This trial will incorporate the following elements:
 - An appropriate number of subjects (e.g. approximately 20 per arm, equal number of males and females 40 to 70 years of age)
 - An appropriate positive control
 - The use of multiple dose levels of rasagiline
 - The use of selegiline as an additional comparator
 - The use of baseline pre-treatment tyramine doses of 25, 50, and 100 mg and dose increments above 100 mg of 100 mg up to 800 mg. Post-treatment tyramine will use a similar dosing as pre-treatment, but starting doses will be lower. Tyramine doses will be administered on separate days
 - The use of blood pressure criterion of three consecutive systolic increases of at least 30 mm Hg with close monitoring at 5 minute intervals over at least 2 hours and collection of at least 3 blood pressure measurements within 15-30 minutes prior to tyramine administration to serve as an integrated average blood pressure for comparison to a threshold pressor response after tyramine
 - Measurement of plasma tyramine at 30 minutes after each tyramine challenge study in all treatment groups.

Protocol submission Date: July 30, 2006

Study Start Date: December 30, 2006

Final Report Submission Date: December 30, 2008

2. To investigate orthostatic blood pressure and pulse timed to rasagiline dosing. This will be evaluated in both the tyramine challenge study listed above and the dose proportionality study listed below (no. 4). The dates of commitments will correspond to the respective dates of the tyramine challenge study and dose proportionality study, respectively.
3. To conduct a thorough QTc study characterizing the effects of rasagiline on cardiac repolarization in humans.

Protocol submission Date: November 28, 2006

Study Start Date: February 28, 2007

Final Report Submission Date: May 31, 2008

4. To investigate the dose-proportionality of daily doses of rasagiline (1, 2 and 6 mg) following multiple-dose administration in healthy young and elderly subjects and the effect of levodopa/carbidopa (single dose) on the pharmacokinetics of rasagiline (multiple dose). A secondary objective of this study will be to evaluate orthostatic blood pressure and pulse rate timed to rasagiline dosing.

Protocol submission Date: January 20, 2006

Study Start Date: March 30, 2006

Final Report Submission Date: February 28, 2007

5. To compare the plasma pharmacokinetic parameters of rasagiline and 1 - aminoindan (1-AI) following once daily repeated dosing of a 1 mg tablet of rasagiline for 8 days in healthy subjects and in subjects with moderate renal impairment.

Protocol submission Date: January 20, 2006

Study Start Date: March 30, 2006

Final Report Submission Date: June 30, 2007

6. To conduct a large, simple, randomized, placebo controlled trial of rasagiline added to standard therapy in approximately 5000 Parkinson's disease patients for a duration of 36 months to assess the relative risk of melanoma.

Protocol submission Date: January 20, 2006

Study Start Date: February 28, 2007

Final Report Submission Date: May 31, 2012 (ongoing review of the data by Data Safety Monitoring Board (DSMB) during the study)

7. To repeat the oral embryo-fetal development study in rabbits. A draft audited report was supplied to Teva by the CRO on March 2, 2006 and is currently under review by Teva.

Protocol submission Date: January 20, 2006

Study Start Date: N/A (Study completed)

Final Report Submission Date: October 31, 2006

8. To conduct a comprehensive review of the literature related to dietary tyramine restrictions including information on the tyramine content of various foods and beverages.

Final Submission Date: November 30, 2006

9. To investigate the effect of levodopa/carbidopa on the pharmacokinetics of rasagiline following multiple-dose administration. This study should also investigate the age and gender effects on pharmacokinetics of rasagiline by enrolling adequate numbers of male and female subjects in different age groups. To exclude the effects of confounding factors, demographic data for the subjects should be carefully collected and recorded.

Protocol Submission Date: September 17, 2006

Study Start Date: November 30, 2006

Final Report Submission Date: October 31, 2007

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 796-1161.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-641

APPROVABLE LETTER(S)



NDA 21-641

TEVA Pharmaceuticals LTD
Attention: J. Michael Nicholas, Ph.D.
Senior Director, U. S. Regulatory Affairs and Pharmacovigilance
425 Privet Road, P.O. Box 1005
Horsham, PA 19044-8005

Dear Dr. Nicholas:

Please refer to your new drug application (NDA) dated and received September 5, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rasagiline mesylate 1 mg Tablet

We acknowledge receipt of your submissions dated:

November 4, 2004	November 18, 2004	January 18, 2004
January 28, 2005	March 2, 2005	March 14, 2005
April 22, 2005	April 28, 2005	May 24, 2005
July 19, 2005		

The November 4, 2004 submission constituted a complete response to our July 2, 2004 action letter.

We completed our review of this application, as amended, and it is approvable.

We continue to be primarily concerned about two issues: 1) the potential for rasagiline to cause melanoma and 2) the possibility that rasagiline may cause hypertensive reactions after ingestion of a high-tyramine content meal.

Melanoma

Although we acknowledge that the data do not present a uniform picture, several observations raise the possibility that rasagiline may increase the risk for melanoma.

First, as we had previously noted, examination of your NDA database reveals a rate of 5.8 tumors/1000 patient-years of exposure, considerably greater than that seen for other Parkinson's treatments for which we have data; this calculation includes only the first 6 tumors reported, prior to the institution of active screening. Inclusion of only these tumors makes comparisons between drugs more appropriate, although it obviously represents a very small data base.

Additionally, a comparison of the tumor incidence in the immediate and delayed start phases of the TEMPO study raises a concern. Specifically, the increase in tumor incidence between these two groups is primarily accounted for by 6 tumors occurring after 24 months of exposure in the immediate start group, compared to none at this time period in the delayed start group. Given the later start in the

latter group, the immediate start group will, on average, have had about 6 months greater exposure. This finding is thus consistent with the expectation that tumor incidence increases with increasing duration of exposure. On the other hand, there is a numerically similar finding in the PRESTO study (more tumors in the immediate start group during the first 2 months of rasagiline exposure) that cannot represent a real drug effect because the rasagiline exposure of the two groups was the same except that the delayed start group received 6 months of placebo before their 12 months of rasagiline. It is therefore possible that these apparently different rates of tumor formation simply represent the variability in the data (and hence no real signal).

Finally, we note that rasagiline is carcinogenic in the mouse (producing lung tumors; although the lowest dose associated with tumors produced an AUC in the mouse about 170 times that seen in humans at an effective dose, the AUC of the no-effect dose was only about 5 fold the human exposure), and positive in in vitro genotoxicity assays in mammalian cells.

On the other hand, in addition to the results of the PRESTO study described above, and the apparent lack of a dose response, other analyses can also argue against the association of rasagiline with an increased risk of melanoma.

In particular, we compared the rate of melanoma diagnoses in EP002 to the rate determined in the American Academy of Dermatology screening program, in which patients were screened a single time by a dermatologist. Overall, including in situ and invasive melanomas, the Observed/Expected ratio for tumors in EP002 was about 5 times that seen in the AAD study. Although there are differences between the patients included in each study, this comparison suggests that patients with Parkinson's disease are at an increased risk for melanoma compared to the general population. A comparison of the rate of melanoma in the rasagiline database (including only those tumors diagnosed after active screening was instituted) to the AAD data yielded a very similar Observed/Expected ratio, suggesting that rasagiline may not have added to the already increased risk associated with Parkinson's disease.

Although the data are admittedly ambiguous, at this time we cannot conclude that the increased rate of melanoma suggested by some of the data is not real. For this reason, and in the absence of a documented advantage of rasagiline over available therapy, we believe the melanoma issue deserves further discussion, analysis, and, possibly, study. We propose to share our detailed analyses with you in anticipation of a discussion about the interpretation of this complex dataset. If we remain unable to determine that it is unlikely that rasagiline is associated with an increase in the risk of melanoma, we would expect to discuss this issue in a public meeting of our advisory committee as soon as is practical.

Tyramine

We continue to believe that you have not provided adequate evidence that a 1 mg dose of rasagiline, taken with a high tyramine content meal, cannot produce hypertensive reactions. Although we recognize that there is no signal for such a risk in the NDA database, we believe that the data you have provided to address this question are inadequate.

As you know, we have serious concerns that the tyramine product you used in all of your challenge studies did not exhibit an appropriate degree of potency/bioavailability. This (among other considerations) calls into question the results of all of these challenge studies. In particular, as we noted in our previous letter, many patients in the Paris study required 800 mg of tyramine for a

threshold response or did not exhibit a blood pressure response to a tyramine dose of 800 mg, an observation in tyramine challenge studies that is unique in our experience. In response, you assert that the literature suggests that a significant proportion of unselected subjects do not respond to such a dose of tyramine (this assertion is primarily based on the description of several challenge studies that excluded subjects who did not respond to doses of tyramine up to 600 mg). You have not, however, presented empirical data showing that any patient has actually ever been excluded from any challenge study because they did not respond to a tyramine dose of 800 mg. For this major reason (and previously expressed concerns that this study enrolled very few patients who showed threshold responses and no elderly subjects), we continue to conclude that the results of the Paris study cannot be considered reliable.

In addition to this concern, there is reason to believe that in your three other tyramine challenge studies, the timing of the post-meal blood pressure monitoring was such that any significant blood pressure elevations might have been missed. Specifically, as we had previously noted, the literature suggests that the maximum increase in blood pressure seen after a meal to which tyramine is added (as was done in your studies) typically occurs at least 2 ½ hours after the meal, times in which the blood pressure monitoring in your studies was relatively sparse. You have presented no clear evidence that this is not the case.

Furthermore, the published literature clearly shows that tyramine doses required to achieve a threshold pressor response increase several fold when tyramine is added to a meal compared to administration under fasting conditions. Thus, one would not expect tyramine threshold responses to the relatively low doses of tyramine used (i.e. 25-75 mg) given with food unless the tyramine sensitivity was markedly increased. In particular, one publication on subjects with increased tyramine sensitivity (increased 5 fold by drug treatment) showed that when tyramine was added to a meal, subjects required 150 mg – 500 mg tyramine to achieve a threshold pressor response despite the fact that a drug had increased fasting tyramine sensitivity several fold. Thus, we have no assurance that the absence of pressor responses in your studies in which tyramine was added to food or administered near a meal represents true negative responses.

In addition, the home blood pressure monitoring in the PRESTO study suffered not only from the deficiency cited above, but also from the fact that the tyramine content of the meals was unknown (not being a challenge study, this would be important information to have in order to interpret the results).

We recognize that you assert that the typical tyramine-rich meal contains far less tyramine than is typically used in formal tyramine challenge studies. This is undoubtedly true, but, for the reasons cited above, we do not believe that you have adequately addressed the effects of rasagiline when given with such a tyramine-rich meal.

Finally, as you know, we believe the data do suggest that there may be an increase in tyramine sensitivity at the 2 mg dose. There is also evidence that some patients who receive a 1 mg dose may achieve plasma levels close to those seen in the typical patient receiving 2 mg (e.g., patients on CYP 1A2 inhibitors, potential non-linearity). This further increases our concerns.

For these reasons, we continue to believe that you must address the question of rasagiline's potential to cause hypertensive reactions in the absence of dietary restrictions prior to approval. As we have said previously, this may be done in Phase 4 if you are willing to adopt labeling requiring dietary tyramine restrictions at recommended doses. A formal fasting tyramine challenge test is the standard way to

evaluate this potential effect. Therefore, we re-iterate our original request to perform a formal tyramine challenge study including the following elements:

- 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, if possible
- 3) Use of an adequately potent tyramine product demonstrated to be bioavailable, (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 selegiline (5 mg BID) as an additional treatment group for comparison to rasagiline
- 6) Use of baseline/pre-treatment tyramine doses of 25 mg, 50 mg, and 100 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 and use otherwise similar dosing as baseline/pre-treatment. Tyramine doses should be administered on separate days.
- 7) Use of a blood pressure criterion of three consecutive systolic increases of at least 30 mm Hg with close monitoring at 5 minute intervals over at least 2 hours and collection of at least 3 blood pressure measurements within 15-30 minutes prior to tyramine administration to serve as an integrated average blood pressure for comparison to a threshold pressor response after tyramine
- 8) Measurement of plasma tyramine at 30 minutes after each tyramine challenge (≥ 25 mg) in all treatment groups pre- and post-treatment
- 9) It is possible that a more ecologically valid test might be acceptable to address your contention that the large doses given in the typical challenge study are clinically irrelevant.

Clinical Pharmacology and Biopharmaceutics

- 1) Please adopt the same method and dissolution specification for the 0.5 mg tablet strength as those adopted for the 1 mg tablet strength.
- 2) Although you have agreed to accept our proposed labeling language regarding the discrepant results for the effect of levodopa on rasagiline clearance, we had asked you to formally evaluate this effect. We continue to believe that an adequate characterization of this effect is necessary.
- 3) We do not believe that you have adequately characterized the dose proportionality of rasagiline. Therefore, we ask you to perform a formal dose proportionality study. This study should enroll at

least 8 subjects (4 males, 4 females) in each age group (40-60; >65 years old) at each dose tested (the study should evaluate at least the following doses: 1 mg, 2 mg, and 6 mg).

- 4) We note a doubling of the plasma levels of rasagiline in patients with mild renal dysfunction compared to normals. Because this finding was unexpected, we believe that patients with moderate to severe renal dysfunction should be formally evaluated (we recognize that you have done so, but we believe the data in these latter patients is unreliable because only a very few patients had adequate plasma sampling).

Clinical

- 1) Although we believe that the blood pressure analyses you have performed are reassuring, you have not presented adequate data on blood pressure in patients with Parkinson's disease appropriately timed to dosing with rasagiline. Therefore, you should perform a study of orthostatic blood pressure and pulse timed to rasagiline dosing. As we noted in our previous Approvable letter, these data can be obtained in your formal tyramine challenge study.
- 2) You have proposed an elevation of CPK of 10 times the baseline as one criterion for deciding that a post-marketing case should be reported as a 15 day report of rhabdomyolysis. We request that you change this criterion to include a change of 5 times the baseline or greater.

Non-clinical

You have attempted to justify the results of your oral embryo-fetal development study in the rabbit by asserting that the low rate of external findings and the lack of visceral findings are consistent with the historical rate in studies performed at the contract laboratory. We do not agree that this is an adequate explanation since, in our experience, these rates are unexpectedly low. For this reason, we ask you to repeat this study.

Chemistry, Manufacturing, and Controls Issues

- 1) We had previously requested that you change the ID test for _____ from HPLC to IR (i.e., like for 1-aminoindan). We again request that you make this change.
- 2) You have set a different R_f specification in the TLC assay for the different tablet strengths. Please adopt a uniform specification, preferably that with a maximum difference o

We have not attached draft labeling pending resolution of the above issues.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We

will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Neurology to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 594-2850.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Robert Temple
8/4/05 05:20:15 PM



NDA 21-641

TEVA Pharmaceuticals, Ltd.
Attention: J. Michael Nicholas, Ph.D.
Sr. Director, U.S. Regulatory Affairs
1090 Horsham Road
North Wales, PA 19544

Dear Dr. Nicholas:

Please refer to your new drug application (NDA) dated and received September 5, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rasagiline mesylate 1 mg Tablet.

We acknowledge receipt of your submissions dated:

November 3, 2003
March 5, 2004

December 23, 2003
May 5, 2004

February 12, 2004

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following concerns.

CLINICAL

Tyramine Studies

We are concerned that the selectivity of rasagiline 1mg/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 2mg 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 mm Hg.
- 7) Measurement of plasma tyramine at 30 minutes after each tyramine challenge (≥ 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 prescribers that patients must restrict their diet so as to avoid food with a high tyramine content.

Melanoma

In our view, the data, taken as a whole, raise concerns that the use of rasagiline may be associated with a risk of melanoma. Although we do not consider the association to have been demonstrated conclusively, we are still sufficiently concerned that, absent additional data, we believe a statement describing the relevant data should be included in product labeling.

In particular, we have concluded that the rates of melanoma detected in your database exceed the rates seen in several epidemiologic databases. Specifically, we have compared the rate of melanoma in your database to that in the SEER and American Academy of Dermatology (AAD) Screening databases.

We acknowledge that there may be underreporting of cases to the SEER database (perhaps about 20%), and that reporting of in situ cases may be particularly problematic. For these reasons, we have compared the rate of only invasive cases in your database to the number that would be expected in a cohort of the size of your database (based on SEER data), making various assumptions about the rate of underreporting to SEER. Even when we assume that the number of cases expected from SEER data is 50% higher than that seen in the actual SEER database (a reasonable estimate based on our assessment of SEER), we still calculated an Observed/Expected ratio of 5.4 (95% CI: 2.2-11.1).

As you note, patients in the SEER database have not been actively screened for melanoma. Patients included in the AAD Screening database, however, have been screened. We therefore compared the rates of melanoma (invasive and in situ) in your cohort with those in the AAD Screening database. In this comparison, we included only those cases in your database whose tumor was detected on the first visit, because, in general, patients in the AAD database were screened only once. When we make this comparison, we obtain a relative risk of about 2.5.

We acknowledge that rates of melanoma are greater in North America than they are in Israel or Argentina, but we do not think this mitigates the findings from the comparisons described above, given that the comparator populations are North American. We further acknowledge an apparent increase in the risk for melanoma in patients with Parkinson's disease compared to that in the general population. However, the observations of this apparent increased risk were made in patients being treated with dopaminergic therapy. Therefore, it is difficult to attribute this increased risk to Parkinson's disease itself; the apparent increased risk might be the result of treatment with dopaminergic drugs. For this reason, we cannot definitively attribute the apparent increased risk of melanoma with your drug to an intrinsic increased risk of melanoma in Parkinson's disease.

As we note above, we have not concluded that these analyses are definitive. We recognize that rates obtained in a database such as yours may not be directly comparable to rates obtained in large epidemiologic databases for many reasons, and that other features of the data raise questions about the relationship (e.g., the relatively short latency for many of the cases, and the observation that there is not a monotonically increasing rate of tumor detection with increasing duration of exposure). Nonetheless, we believe the signal is of sufficient strength to warrant a statement in labeling, as well as to request the additional information below:

- The dose-response relationship for melanoma was not well described in the NDA submission. Please present a dose response analysis for melanoma occurring in association with rasagiline treatment. The denominator should be in person-year units and should reflect time contributed by patients to each dose received (e.g., if a patient was treated with 0.5 mg initially and then later increased to 1 mg, the time they were treated with each dose should be allotted to that dose).

- You have provided some evidence that melanoma is more common in patients with Parkinson's disease. We would like to perform an analysis comparing two populations, both subject to active surveillance for melanoma: the American Academy of Dermatology cohort and the cohort of North American Parkinson's disease patients that you studied. We have the data for the AAD cohort broken down by age and gender; we ask that you submit the incidence of melanoma from the North American cohort study EP002 broken down by the following age categories (<45, 45-54, 55-64, 65-74, 75+, for invasive and in situ tumors separately) and gender. Our Safety Group will perform the analyses.
- We ask that you perform a pooled analysis of all patients randomized in the North American studies, TEMPO and PRESTO. For all patients randomized to rasagiline or placebo we ask that you include all melanomas ascertained in those patients throughout the placebo-controlled phases, the active-controlled phases, and even the open-label extensions. We ask that you compare the numbers of melanomas observed throughout all the above 3 phases for the two groups: 1) patients randomized to rasagiline from the start, and 2) patients with a "delayed start" of rasagiline.

Finally, we recommend that you conduct a large simple randomized controlled trial, post-approval, to compare melanoma rates between Parkinson's disease patients who are exposed and unexposed to rasagiline. A randomized controlled trial is suggested as this design has the greatest likelihood of producing equivalent treatment and control groups. Parkinson's disease patients (both newly diagnosed and those already on levodopa therapy) could be recruited through their outpatient providers, but it would be beneficial to stratify patients by monotherapy or adjunctive therapy. To control for geographic variation in background rates, it is recommended that similar numbers of rasagiline exposed and unexposed subjects be drawn from various geographic areas within North America. Given the much lower risk of melanoma among persons with increased melanin content in their skin, subject recruitment should be restricted to Caucasian subjects. Baseline information for cohort members should include demographic information, information on melanoma risk factors and past diagnosis of skin cancer, as well as information on current and past Parkinson's disease therapies. Subjects would then be monitored through questionnaires (yearly or twice a year) inquiring about interim changes in Parkinson's disease therapies. You should conduct active screening for melanoma (once every six months), as detection is likely to vary in different clinical settings. Upon study entry, subjects should also be given basic information on skin cancers and self-examination for suspicious lesions. Other aspects of trial design, including sample size and duration, can be decided upon through further discussion between TEVA and DNDP.

Additional Analyses:

1. Additional ECG Analysis

Guidance is evolving in CDER (and ICH) requesting that all new drug products in development be adequately evaluated to characterize the effect of the drug on cardiac repolarization. The “thorough QT” study is described in a recently completed ICH Step 2 guidance (ICH-E 14). Given that the rasagiline development program did not include an adequate assessment of the effect of rasagiline on the QT/QTc interval (or the other ECG parameters, for that matter), a two pronged approach is requested.

- In order to understand the effect of rasagiline on the ECG as measured in Parkinson’s disease (PD) patients on rasagiline monotherapy, we request that the ECGs from TEMPO be centrally re-read and analyzed in a manner similar to how the PRESTO and LARGO studies in Cohort 2 have been analyzed.
- In order to understand the effect of rasagiline on cardiac repolarization in general, we request that you conduct a “thorough QT” study similar to the one described in the concept paper referenced above. Whether this needs to be completed prior to approval will depend on the TEMPO analysis and overall results in all three controlled studies. However, you may wish to incorporate EKG monitoring into the tyramine challenge study, as with blood pressure monitoring (see below).

It is also requested by the Office of Clinical Pharmacology and Biotherapeutics that an ECG dataset be created for subjects in TEMPO, PRESTO and LARGO that would contain the following variables: rasagiline dose, concentration, time on rasagiline, heart rate (HR), RR (1/HR), QT, and all demographic covariates (i.e., sex, age, etc.).

2. We believe it is important to characterize changes in blood pressure timed to dosing, ideally capturing results at Tmax, as well as at other appropriate times during the dosing interval. Such data was not collected in your trials. We ask that you collect such data for both resting BP and orthostatic BP. We believe this data can be collected within the tyramine challenge study requested above, with a placebo-control group and BP measured at multiple timepoints after dosing.

3. Additional Analysis of Flu Syndrome

Flu syndrome and musculoskeletal adverse events were commonly reported with rasagiline treatment. In Cohort 1, the adverse events of flu syndrome, rhinitis, conjunctivitis, neck pain, arthralgia, arthritis, and joint disorder were all reported at least twice as frequently in the rasagiline group as in the placebo group. In Cohort 2, this rasagiline associated excess was observed for flu syndrome, neck pain, and arthralgia.

The frequency of these phenomena warrants further evaluation, as the NDA does not provide significant analysis or commentary on this potential safety signal. You should therefore perform additional analyses exploring the nature of this potential syndrome. We would be happy to discuss with you approaches to this re-analysis. In particular, we would be

interested in your examining the frequency of amantadine as a concomitant PD therapy, as this drug is also an antiviral agent. An imbalance in the use of amantadine between treatment groups may have affected the occurrence of flu syndrome. In vitro or preclinical studies may be performed to investigate the role of cytokines as a potential mediator of these symptoms.

4. Laboratory and Vital Sign Data

4a. For the laboratory and vital sign data, please provide an analysis of mean change from baseline to subject's *Maximal* Observed Value for the various parameters.

4b. For the analysis of Potentially Clinically Significant (PCS) values for both laboratory and vital sign data, please clarify whether all values were evaluated on PCS criteria, or only the LOV. If LOV only, please repeat the laboratory and vital sign analysis evaluating on the PCS criteria.

5. Increased Attribution of Discontinuations to a Specific Adverse Event (AE)

For approximately 7% of discontinuations in the rasagiline development program, the discontinuation was not attributed to a specific AE. Additional measures should be taken to identify the AE associated with discontinuation for a particular subject. This may include evaluating a listing of all AEs reported by discontinuing subjects along with the dates of their AEs and discontinuation. The frequency table for adverse events leading to discontinuation should be updated with the additional information.

6. Postmarketing Rhabdomyolysis Surveillance

The two cases of rhabdomyolysis occurring during the rasagiline development program both followed a fall and prolonged immobilization, and one lacked laboratory (CPK) confirmation. These two cases do not appear to represent a significant safety signal, but close monitoring in the postmarketing period is recommended, and it is requested that 15-day reports be submitted for any cases of CPK increased, myalgia, myopathy, rhabdomyolysis, and related adverse events in the postmarketing period

Labeling Recommendations:

1. Restriction of Cohort 2 Adverse Event Tables in Labeling to PRESTO only

The adverse event reporting rates for the two levodopa adjunct studies combined in Cohort 2 (PRESTO and LARGO) varied considerably, with substantially higher rates reported for PRESTO. Given this large difference in rates and that the data from the North American study PRESTO are presumably more representative of the United States Parkinson's Disease patient population, it is recommended that the Adverse Events labeling tables for rasagiline as levodopa adjunct treatment should include PRESTO data only.

2. Update Labeling to Reflect Changes from AE Re-Coding

The Adverse Reactions section of the proposed labeling was prepared prior to the FDA request to re-code the verbatim terms for certain preferred terms. This re-coding has changed the percentage of subjects affected by some of the adverse events, and the tables and AE frequency lists should be revised to reflect these shifts in AE incidence.

CHEMISTRY, MANUFACTURING, AND CONTROLS ISSUES (CMC):

1. We note that we have included 0.5 mg as a recommended dose in the adjunctive setting in product labeling. For this reason, we ask you to submit a comprehensive CMC package to support this dosage form.
2. You have requested, and are granted, a Categorical Exclusion to the Environmental Assessment.
3. The proposed expiry period of 36 months for the 1 mg tablets and 24 months for the physician/promotional package is acceptable.
4. The ID test for 1-aminoindan is identical to the assay test; that is, both test methods are HPLC-based. We recommended that you develop a more specific ID test method since related materials may have similar HPLC retention times. As an example, a useful ID test would be USP <197>, ID by spectroscopic methods or USP <201>, thin layer chromatography. Using this strategy, the [proposed] TLC test becomes an ID test while the HPLC test acts as an assay/confirmatory test.
5. Please make the appropriate changes in the Analytical Specifications and Stability Testing Program regarding dissolution specifications. These changes are delineated in the Clinical Pharmacology & Biopharmaceutics section of this correspondence.

NONCLINICAL

1. For the 2-year carcinogenicity study in rats, you need to conduct microscopic analysis of a full battery of tissues in the low and mid-dose groups. This additional analysis is needed because the high dose, although not associated with an increase in any tumor type, was associated with an excessive decrease in body weight (relative to controls). That is, the high dose exceeded a maximally tolerated dose, defined as a >10% decrease in body weight relative to controls. This request has previously been provided to you in the minutes of the Executive Carcinogenicity Committee meeting held on June 8, 2004.
2. AGILECT™ is a mesylate salt and, therefore, potential genotoxic impurities (e.g. _____) may arise during synthesis of the drug substance and/or during storage. In particular, the potential presence of the following in the drug substance and/or drug product is of concern:
 - (a) _____ : (and related impurities) in the drug substance _____ These compounds are considered to have genotoxic potential based on structural alert.
 - (b) _____, a known mutagen, in the drug substance due to the _____
 - (c) _____ in the drug product. You have demonstrated this compound to be positive in an *in vitro* Ames test.

Ideally, the above compounds, known to be mutagenic, should be eliminated. If that is not possible, specifications should be set for each compound at \leq _____. The same is true for _____ (and related impurities); however, since we presume these to be mutagenic (i.e., mutagenicity has not been demonstrated), you may choose to directly test each of these compounds in an *in vitro* Ames assay and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay (with colony sizing). If they are negative in these assays, there would be no need to reduce the levels to \leq _____. You need to provide details of the method(s), including limits of detection and quantitation, used to evaluate each compound.

3. There is concern as to the adequacy of the oral embryo-fetal development study conducted in rabbit (_____ Project No. 671411). This concern is due primarily to the low incidence of external findings and a lack of visceral findings in rabbit fetuses in the study. This would suggest reduced sensitivity to detect soft tissue abnormalities, variants, etc. Unless data can be provided that adequately document the sensitivity of the methods used to assess fetal effects, the study will need to be repeated.

LABELING, PACKAGING AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Agilect, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement which might minimize potential user error.

A. GENERAL COMMENTS

1. The lettering on the background is difficult to read. DMETS recommends revising the color to improve legibility.
2. The strength of this product is based on the active moiety Rasagiline and not the salt Rasagiline Mesylate. Additionally the dosage form (tablet) should appear in conjunction with the established name. Therefore, we recommend one of the following presentations:
 - a. Agilect
(Rasagiline Tablets)
1 mg
 - b. Agilect
(Rasagiline Mesylate Tablets)
equivalent to 1 mg of Rasagiline
 - c. Agilect
(Rasagiline Mesylate Tablets)
1 mg*

*Each tablet contains Rasagiline Mesylate equivalent to 1 mg of Rasagiline.
Note: DMETS prefers the first option because this nomenclature is consistent with USP recommendations on 'labeling of salts of drugs'.
3. Relocate 'Rx only' to the principle display panel.
4. Revise the "Each tablet contains..." statement to read "Each tablet contains Rasagiline Mesylate equivalent to 1 mg Rasagiline".
 - a. Container Label (30 count):
 1. See general comments A1 through A3.
 2. Relocate the net quantity so that it does not appear in close proximity to the product strength.
 3. Your proposed container of 30 tablets appears to be 'Unit of Use' packaging. Please indicate whether the container has a child resistant closure.
 4. Include a usual dose statement.

B. Container Label (7 count sample).

1. See A2 and B2.
2. From the draft container label provided, it appears that the proprietary and established names appear two times on the foil topside.
3. In the current presentation, once a patient punches out a tablet, the proprietary and established name may no longer be readable. Each individual tablet (blister) must be labeled with the proprietary and established name, strength, lot #, and expiration date.
4. We note that the professional sample blister pack was submitted in black and white.

Thus, DMETS did not have the opportunity to evaluate and comment on the use of colors, color logo, color fonts and graphics, etc.

5. Add the statement "RX ONLY" to the principle display panel.
 - a. Carton Label (7 count sample).
 1. See general comments A1 through A4.
 2. Please indicate whether the carton is child-resistant.
 - b. Package-insert labeling:
 1. See general comment A2.

C. Nomenclature

DMETS has no objections to the use of the proprietary name, Agilect. This is considered a tentative decision and this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to the NDA approval will rule out any objections based upon approvals of other proprietary or established names from the date of this document.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

1. You need to formally evaluate the effect of levodopa on rasagiline clearance.
2. Please adopt the following dissolution method and specification for the 1mg strength of rasagiline tablets:

Equipment USP, → Apparatus 2 (Paddles),
Dissolution volume 500 mL.
Medium 0.1N HCl (aq.)
Rotation speed 50 rpm
Temperature 37°C
Sampling time 15 minutes
Dissolution Specification Q= — in 15 min

In addition, it will be necessary for you to submit draft printed labeling revised according to the attached labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 594-2850.

Sincerely Yours

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

25 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓
___ § 552(b)(4) Draft Labeling

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

/s/

Robert Temple
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