CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-641

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

TEVA NEUROSCIENCE

1.3.2 Patent Certification for NDA 21-641

Not Applicable.

1090 Horsham Road • PO Box 1090 • North Wales, PA 19454-1090
Toll Free (800) 392 6985 • Toll Free FAX: (800) 862 3003 • FAX: (215) 591 8826

EXCLUSIVITY SUMMARY

NDA # 21-641 SUPPL # HFD # 120

Trade Name Azilect

Generic Name rasagiline mesylate

Applicant Name TEVA Pharmaceuticals

Approval Date, If Known May 17, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐

Explain:

Investigation #2

IND # YES ☐ NO ☐

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Teresa Wheelous
Title: Sr. Regulatory Management Officer
Date: May 8, 2006

Name of Office/Division Director signing form: Dr. Russell Katz
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Russell Katz
5/9/2006 08:04:57 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-641 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: 9/5/2003 **Action Date:** 5/17/06

HFD -120 **Trades and generic names/dosage form:** Azilect (rasagiline mesylate)

Applicant: Teva Pharmaceuticals **Therapeutic Class:** NME (1)

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: _ for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa. ___

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

X Disease/condition does not exist in children

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-641
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Teresa Wheelous, Sr. Regulatory Project Manager

cc: NDA 21-641
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Russell Katz
5/17/2006 05:09:13 PM

TEVA NEUROSCIENCE

August 4, 2005

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Document Control Room (HFD-120)
Food and Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

NDA 21-641
AGILECT® (rasagiline mesylate) Tablets
Amendment to a Pending Application

Dear Dr. Katz:

Reference is made to the NDA application cited above, originally submitted on September 5, 2003.

The purpose of this electronic submission is to formally supply a response to a FDA request for information. On August 3, 2005, the Division requested a revised debarment certification be supplied for the application. This submission provides the signed certification as requested by the Division.

All electronic files included in this submission are provided on one CD-ROM and the electronic submission is approximately 1 MB. All files were checked and verified to be free of viruses, prior to being written to CD using Trend Micro Office Scan Corporate Edition, program version 6.5 and virus pattern file number 2.749.00 with a virus pattern release date of July 27, 2005.

If you have any questions or require any further assistance, please do not hesitate to contact me.

Regards,

Dennis Williams, R.Ph.
Sr. Manager
Regulatory Affairs

425 Privet Road • PO Box 1005 • Horsham, PA 19044-8005
Toll Free (800) 392 6985 • Toll Free FAX: (800) 862 3003

1.3.3 Debarment Certification

NDA 21-641
Agilect® (rasagiline mesylate) tablets

Pursuant to Section 306 (K) (1) of the Federal Food, Drug and Cosmetic Act (here after referred to as the Act), Teva Neuroscience, Inc. certifies that the applicant did not and will not use in any capacity the services of any person debarred in subsections 306 (a) and (b) of the Act, in connection with this application

J. Michael Nicholas, Ph.D.
Sr. Director, U.S. Regulatory Affairs and
Pharmacovigiliance
Teva Neuroscience, Inc.

8/3/05
Date

425 Privet Road • PO Box 1005 • Horsham, PA 19044-8005
Toll Free (800) 392 6985 • Toll Free FAX: (800) 862 3003

1.3.3 Debarment Certification for NDA 21-641

AGILECT® (rasagiline mesylate) 1mg Tablets

Pursuant to Section 306(K)(1) of the Federal Food, Drug and Cosmetic Act (here after referred to as the Act), Teva Neuroscience, Inc. certifies that, to the best of its knowledge and belief the applicant did not and will not use in any capacity the services of any person debarred in subsections 306 (a) and (b) of the Act, in connection with this application.

J. Michael Nicholas, Ph.D.
Senior Director, U.S. Regulatory Affairs
and Pharmacovigilance
Teva Neuroscience, Inc.

9/5/03
Date

901 E. 104th Street, Suite 900 • Kansas City, MO 64131
Phone: (800) 221-4026 • Fax: (816) 508-5016

NDA ACTION PACKAGE CHECKLIST
Volume 1

NDA 21-641		
Drug: **Azilect (rasagiline mesylate) 1 mg Tablet**	Applicant: TEVA Pharmaceuticals	
RPM: CDR Teresa Wheelous	HFD- 120	Phone # 301-796-1161
Application Type: **(X)** 505(b)(1) **( )** 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	**(X)** Standard **( )** Priority
• Chem class (NDAs only)	NME (1)
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**May 17, 2006**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) **( )** Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(X)** No
• This application is on the AIP	**( )** Yes **(X)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
A Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
B Patent	
• Information: Verify that form FDA-3542a was submitted.	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	**N/A**
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	**( )** Verified
C Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	**( )** Yes, Application #_____ **(X)** No

D Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	5/5/06
[redacted]	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
E Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	7/14/05 DDMAC, 1/21/04 DMETS / DDMAC, 5-17-06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
F Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
G Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
H Outgoing correspondence (i.e., letters, E-mails, faxes)	
I Memoranda and Telecons	
J Minutes of Meetings (IND 45,958)	
• EOP2 meeting (June 18, 1997)	
• Pre-NDA meeting(April 30, 2003)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other – Malignant Melanoma (April 6, 2001); internal meeting 1/29/04Tyramine Restricted Diet (August 17, 2000 & August 23, 2000) • End of Review Meeting 9/27/04 • Rat Carcinogenicity Datasets Need Correction 5/9/05	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

K Summary Reviews Division Director- 7/1/04 , 7/23/05, 5/16/06 Medical (Efficacy) Team Leader - 7/22/05, 6/25/04 Medical (Safety) Team Leader – 6/25/04	
VOLUME 2	
L Clinical reviews –Efficacy – 7/18/05 (draft), 6/18/04	
M Safety Update review(s)	7/18/05, 6/25/04
Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	
Pediatric Page(separate page for each indication addressing status of all age groups)	Waived
Demographic Worksheet *(NME approvals only)*	
VOLUME 3	
N Statistical review(s) *(indicate date for each review)*	6/2/04
O Biopharmaceutical review(s) *(indicate date for each review)*	7/12/05, 4/15/05, 4/6/05, 5/13/04, 11/3/03, 5/9/06
Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	n/a
P Clinical Inspection Review Summary (DSI)	
Clinical studies	
Bioequivalence studies	
Q CMC review(s) *(indicate date for each review)*	7/ /05, 5/14/04
Environmental Assessment	
Categorical Exclusion *(indicate review date)*	
Review & FONSI *(indicate date of review)*	
Review & Environmental Impact Statement *(indicate date of each review)*	
Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
VOLUME 4	
R Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* Team Leader 7/1/04 Reviewer 6/25/04	
Nonclinical inspection review summary	
Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	7/24/05, 2/9/04
CAC/ECAC report	6/14/04

A2

4 Page(s) Withheld

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

__ § 552(b)(5) Deliberative Process

__ § 552(b)(4) Draft Labeling

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: May 11, 2006	**DESIRED COMPLETION DATE:** May 11, 2006 **PDUFA DATE:** May 17, 2006	**ODS CONSULT #:** 03-0142-2

TO: Russell Katz, M.D.
Director, Division of Neurology Products

THROUGH: Linda Kim-Jung, Pharm.D. Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Laura Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Azilect**
(Rasagiline Mesylate Tablets)
0.5 mg and 1 mg

NDA #: 21-641

SPONSOR: Teva Neuroscience, Inc.

RECOMMENDATIONS:

1. Limited data was available to complete a comprehensive analysis of the proprietary name, Azilect. Although a limited analysis was conducted, DMETS does not recommend the use of the proprietary name, Azilect.

   Additionally, due to recent post-marketing reports of global product confusion we recommend that the sponsor be made aware of existing products in the foreign marketplace with tradenames having the identical and similar spelling to Azilect; and that the sponsor consider submitting an alternate proprietary name. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names form the signature date of this document

2. DDMAC finds the name, Azilect, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Diane Smith at 301-796-0538

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 15, 2006

NDA NUMBER: 21-641

NAME OF DRUG: **Azilect**
(Rasagiline Mesylate Tablets)
0.5 mg and 1 mg

NDA SPONSOR: Teva Neuroscience, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION

This consult was written in response to request from the Division of Neurology Products (HFD-120) for a review of the proprietary name, Azilect. This is the second proprietary name review for this new drug application (NDA). In our first review, dated January 21, 2004, (ODS Consult # 03-0142), DMETS did not have any objections to the use of the first proposed proprietary name, Agilect. However, the Division of Drug Marketing, Advertising and Communications (DDMAC) objected to the proposed proprietary name, Agilect from a promotional perspective. Despite DDMAC's concerns, the Division of Neurology Products allowed the sponsor to continue to use the tradename Agilect. Subsequently, in DMETS' second review of the proposed proprietary name, Agilect (ODS Consult # 03-0142-1 dated July 25, 2005), DMETS identified the proposed proprietary name Angeliq (NDA 21-355) as having the potential for confusion with Agilect. However, DMETS had no objections to the use of the proprietary name, Agilect, as long as only one of the names (Angeliq vs. Agilect) was approved. At that time the Division of Neurology Products informed the sponsor that they would need to submit an alternate name. Additionally, we note that the proprietary name, Angeliq was approved on September 28, 2005. Therefore, the sponsor has subsequently submitted an alternate proposed proprietary name, Azilect, for review and comment by DMETS. The container labels, carton, and insert labeling were reviewed in our previous two name reviews.

PRODUCT INFORMATION

Azilect is a propargylamine-based drug indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy. The recommended initial dose of Azilect is 1 mg administered orally once daily as monotherapy or 0.5 mg administered once daily when used as adjunctive therapy. Azilect is proposed to be available as 0.5 mg and 1 mg tablets in bottles of 30 count tablets.

II. RISK ASSESSMENT

Since this was a priority review and in order to meet the Division's requested completion date and the PDUFA date, DMETS was not able to perform a full comprehensive routine analysis of the name, Azilect. Thus, this review does not include our prescription analysis study. The DMETS' safety evaluator was only able to conduct a limited search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii-iv] for existing drug names which sound-alike or look-alike to Azilect to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[v] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[vi] were also conducted.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proposed proprietary name. Potential concerns regarding drug marketing and promotion related to the proposed name are also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the name, Azilect, acceptable from a promotional perspective.

2. The Expert Panel identified fourteen proprietary names that were thought to have the potential for confusion with Azilect. These products are listed in table 1 (see pages 4-5), along with the dosage forms available and usual dosage.

[i] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

[iv] FDA's Phonetic and Orthographic Computer Analysis (POCA)

[v] WWW location http://www.uspto.gov.

[vi] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Azilect	Rasagiline Tablet: 0.5 mg, 1 mg (30 ct)	One tablet orally once daily. The recommended starting doses are 1 mg for monotherapy and 0.5 mg for adjunct therapy.	N/A
Acutect	Technetium Tc-99m Apcitide Injection: 20 mCi contains 100 mcg of bibapcitide radiolabeled with 20 mCi of technetium 99m.	Peripheral IV injection in an upper extremity at a dose of approximately 100 mcg of bibapcitide radiolabeled with 20 mCi of technetium 99. Imaging should begin between 10 and 60 minutes following injection.	LA
Azelex	Azelaic acid Cream: 20% 30 g and 50 g tubes	Apply cream in a thin film to the affected area twice daily, morning and evening.	LA/SA
Aricept **Aricept ODT**	Donezepil Tablets: 5 mg, 10 mg Orally Disintegrating Tablets: 5mg, 10 mg Oral Solution: 1 mg/mL	Initially, 5 mg PO once daily. Steady state is not reached until 15 days of any given dosage. Upward titration should not occur until at least 4—6 weeks; then may increase to 10 mg PO once daily if needed	LA
Acilac	Lactulose Solution: 10 g/15 mL	For the treatment of hepatic encephalopathy : Initially, 30—45 ml (20—30 g of lactulose) PO, given 3—4 times per day. If necessary, hourly doses of 30—45 ml PO may be given until a laxative effect is induced. Once a laxative effect has been established, dosage should be reduced to produce 2—3 loose stools daily. Rectal dosage: Initially, 300 ml lactulose, diluted with 700 ml water or normal saline, and administered via rectal balloon catheter and retained for 30 to 60 minutes. May repeat every 4—6 hours as needed. If the enema is evacuated too promptly, it may be repeated. Oral therapy should replace rectal as soon as possible. For constipation: Initially, 15—30 ml PO once daily, increasing to 60 ml PO once daily if needed.	SA
Abelcet	Lipid Complex Amphoterecin B Supension for Injection: 5 mg/mL	For the treatment of invasive fungal infections in patients refractory or intolerant to conventional amphotericin B deoxycholate therapy, including aspergillosis, candidemia, and cryptococcosis infection: Adults and children: 5 mg/kg/day as a single IV infusion. The rate of infusion should be 2.5 mg/kg/hr.	LA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Azilect	Rasagiline Tablet: 0.5 mg, 1 mg (30 ct)	One tablet orally once daily. The recommended starting doses are 1 mg for monotherapy and 0.5 mg for adjunct therapy.	N/A
		For immunocompromised patients who do not clear parasites or who experience relapses, expert advice regarding further treatment is recommended. Intravenous dosage Adults and children: A dose of 2 mg/kg IV once daily for 7—10 days has been utilized. Intravenous dosage (amphotericin B lipid complex): Adults and children: Doses of 1—3 mg/kg/day IV for 5 days have been used for the treatment of visceral leishmaniasis that failed to respond to or relapsed after treatment with an antimony compound.d 2 hours.	
Cylert	Pemoline Tablets: 18.75 mg, 37.5 mg, 75 mg Chewable Tablets: 37.5 mg Cylert tradename and generic pemoline no longer marketed in the U.S. due to safety reasons.	Adults, adolescents, and children ≥ 6 years: 37.5 mg PO as a single dose each morning. Increase at weekly intervals by ≤ 18.75 mg/day until the required response is obtained. Usual effective dosage range 56.25—75 mg/day PO.	LA
Aziliv (Brazil)	Ranitidine Hydrochloride	Further information not available	LA
Aciloc (Thailand, India)	Ranitidine Hydrochloride	Further information not available	LA/SA
Aciloc (Denmark, Sweden)	Cimetidine	Further information not available	LA/SA
Azelac (Greece)	Azalaic Acid	Further information not available	LA/SA
Acilax (Hong Kong)	Acyclovir	Further information not available	LA
Aciphex	Rabeprazole sodium Delayed-release tablets: 20 mg	20 mg to 40 mg orally once daily.	LA
Tazicef	Ceftazidime Hydrochloride Powder for Injection: 1 g, 2 g, 6 g	1—2 g IV/IM every 8 hours. The higher doses should be used in serious gynecologic and intra-abdominal infections, meningitis, or severe life-threatening infections, especially in immunocompromised patients. The usual maximum dosage is 6 g/day.	LA

*Frequently used, not all-inclusive.
*****NOTE: This information is confidential and is not FOIable.**

C. SAFETY EVALUATOR RISK ASSESSMENT

Limited time and data were available to complete a comprehensive analysis of the proprietary name, Azilect.

In reviewing the proprietary name "Azilect", the products considered to have potential for name confusion with Azilect include: Acutect, Azelex, Aricept, Acilac, Abelcet, Aciphex, Tazicef, Cylert, Aziliv (Brazil), Aciloc (Thailand, India), Aciloc (Denmark, Sweden), Azelac (Greece), and Acilax (Hong Kong). Upon review of the names Aciphex and Tazicef, it was determined that these names lacked convincing look-alike/sound-alike similarities with Azilect in addition to numerous different product characteristics such as the dosage form, product strength, indication for use, route of administration and/or frequency of administration and will not be discussed further.

The name — was a proposed proprietary name — reviewed by DMETS (ODS consult , IND — on May 11, 2005. In the review, DMETS did not recommend the use of the name — The sponsor subsequently submitted alternate proposed names for this product and it was approved as Osmoprep. Thus, the name — is no longer under active consideration and will not be discussed further.

The proprietary name Cylert has been discontinued. In May 2005, the sponsor chose to stop selling Cylert in the United States due to the risk of liver toxicity. Additionally, all generic companies have agreed to stop sales and marketing of the generic pemoline drug product. DMETS believes that it is not likely that Cylert or pemoline tablets will ever be marketed again in the United States and thus, Cylert will not be reviewed further.

The foreign proprietary names Aziliv (Brazil), Aciloc (Thailand, India), Aciloc (Denmark, Sweden), Azelac (Greece), and Acilax (Hong Kong) were identified as having look-alike or sound-alike properties to the proposed proprietary name, Azilex. Dosage form and dosing information pertaining to these products was unavailable in numerous drug information resources, including the Internet. The Aziliv (Brazil) and Aciloc (Thailand/India) names are Ranitidine Hydrochloride products. A second product named Aciloc is marketed in Denmark and Sweden, but this product contains Cimetidine. The Azelac (Greece) name is a marketed Azelaic Acid topical product. Finally, Acilax (Hong Kong) is a marketed Acyclovir product. Through literature review and postmarketing surveillance, DMETS is aware of confusion between products marketed domestically and abroad which have similar or identical proprietary names, but different active ingredients. A recent example of such confusion is the case of Palladone (U.S. extended-release hydromorphone) vs. Pallidone (New Zealand – methadone). Additionally, the Institute of Safe Medication Practices (ISMP) also recently published an article citing other such examples of confusion, including, Dilacor XR (U.S. – extended-release diltiazem) vs. Dilacor (Serbia – digoxin). DMETS recommends that the sponsor be made aware of these foreign products with the proprietary names, Azilect, and that based on this existence they should consider submitting an alternate name.

1. Azelex was identified as having similar orthographic and phonetic characteristics with Azilect. Azelex is indicated for the treatment of Acne Vulgaris. These two names may sound-alike when pronounced, particularly if the 'agi' of Azilect and the 'aze' of Azelex are pronounced using the 'asha' sound. The next three letters may also sound similar: 'ele' vs.'ile'. Azelex and Azilect may look-alike when scripted (see below). Each name begins with the letter 'a' and the second letter of both names may have a downstroke (z vs. g) which contributes to look-alike similarities between the

two names. Additionally, the middle portion of name (-ele- vs. -ile-) may look similar if the dot above the "i" for Azilect is not prominent or if the letter "e" in Azelex is not written clearly. Differences in product characteristics which may help to distinguish both names include dosage form (tablet vs. topical cream), and route of administration (oral vs. topical). Although, the dosing frequencies (daily vs. twice daily) and strengths are different for the two drugs, postmarketing evidence has shown that confusion may occur when two names look similar with the aforementioned differences. For example, the currently marketed products Visicol and Vesicare have been confused despite differences in strength (1.5 gm vs. 5 mg or 10 mg) and dosing frequency (every 15 minutes vs. once daily) Since Azilect and Azelex are available in a single dosage form, this information may be omitted on a prescription order. Additionally, Azilect is supplied in bottles of 30 tablets while Azelex is available as 30 g and 50 g tubes. It would be possible for a prescription containing the quantity "#30" to be dispensed as a bottle of 30 tablets of Azilect or as a 30 gm tube of Azelex. Postmarketing experience also has shown that practitioners may not be aware of newly marketed products and often dispense an incorrect product due to similarities in spelling with an existing product. Thus in this case, Azelex is a well recognized name and may be inadvertently dispensed for Agilect. Furthermore, topical products such as Azelex are often prescribed with the directions "as directed" (UD). In which case 'UD' could be misinterpreted as 'QD'. Therefore, it would be difficult to differentiate between a prescription for "Azelex UD #30" and "Azilect QD #30" if the strengths is omitted or misinterpreted. Despite the different product characteristics between this name pair, of which some can be omitted, the overwhelming similarities increase the potential for confusion. Therefore, DMETS does not believe that both names should co-exist in the marketplace.

Azelex
Azilect

2. Aricept was identified as having similar look-alike characteristics with Azilect when scripted. Aricept is indicated for mild to moderate dementia of the Alzheimer's type. Both names begin with the letter 'a' and contain four of the same letters 'c, e, i, t' which contributes to the look-alike characteristics between the name pair. However, when scripting, Azilect may have a downstroke with the letter "z" and two upstrokes with the letters "l and t" which may help to differentiate the two names. Aricept, on the other hand only contains one upstroke (the letter "t"). The two names share some product characteristics such as the dosage form (tablet), unit of measure (mg) and dosing frequency (once daily). Although the products are available in different strengths, DMETS notes that the available strengths for both products share the same numerals (5 mg vs .5 mg and 10 mg vs. 1.0 mg,for Aricept and Azilect respectively) which may look similar if the decimal point is overlooked and a trailing zero is present. This creates the potential for misinterpretation and confusion which may lead to medication errors. Orthographic similarities in conjunction with similar product characteristics increase the potential for confusion. Therefore, DMETS does not believe that both names, Aricept and Azilect, should co-exist in the marketplace.

Aricept
Azilect

3. AcuTect was identified as looking similar to Azilect when scripted. AcuTect is a radioactive imaging test kit including Technetium Tc-99m Apcitide Injection which is used to diagnose acute venous thrombosis in the legs. The two names have some orthographic similarities. Each name begins with the letter 'A', ends with the suffix '-ect', and contains seven letters. Therefore, they can look similar when scripted. However, the products differ in route of administration, (oral vs. intravenous), dosage form (tablet vs. injection), dose (0.5 mg or 1 mg vs. standard dose of 100 mCi containing 100 mcg of bibapcitide radiolabeled with 20 mCi of technetium 99m), dosing frequency (daily vs. one time), dosage units (mg vs. mCi), packaging (bulk bottle vs. kit), and storage area (pharmacy shelf vs. refrigerator). Azilect is a tablet which does not require refrigeration, but AcuTect must be stored under refrigeration. Therefore, AcuTect will not be stored near Azilect on pharmacy shelves which minimizes the potential for selection error. Despite some orthographic similarities between Azilect and AcuTect, DMETS believes that the product characteristics such as the routes of administration, dosage form, dose, dosing frequency, packaging, and storage conditions, makes it unlikely that Azilect and AcuTect will be confused for one another.

azilect
acutect

4. Acilac may sound like Azilect depending upon how they are pronounced. Acilac is a brand of lactulose oral solution (10 g/15mL) which is used orally for constipation or orally/rectally for the treatment of hepatic encephalopathy. The beginnings of both names can sound identical when spoken ('a-cil-' vs. 'a-zil-'), especially if both of the letters 'a' are pronounced as a hard letter 'a'. Additionally, the endings of both names can sound similar when spoken ('-lac' vs. '-lect') especially if the letter 't' in Azilect is not prominently pronounced. However, there are differentiating product characteristics that help distinguish between the two names such as; dosage form (tablets vs. oral solution), strength (0.5 mg or 1 mg vs. 10 g/15 mL), and unit of measure (milligrams vs. grams). Azilect is available in two strengths (0.5 mg or 1 mg) and so a strength should be specified on the prescription. However, Acilac is available in one strength so the strength may not be specified on a prescription. When Acilac is prescribed for the treatment of hepatic encephalopathy, a specific regimen is used and doses are titrated to stool production, so a prescription for Acilac may contain additional directions for use that may help differentiate it from a prescription for Azilect. When Acilac is prescribed for constipation, it is administered daily. However, verbal prescriptions for either product should contain a differentiating unit of measure for the dose, such as milligrams or number of tablets for Azilect and grams, number of tablespoons, or milliliters for Acilac. Thus, despite some phonetic similarities between the two names, differentiating product characteristics such as the dosage form, strength, or unit of measure, makes it unlikely that Azilect and Acilec will be confused for one another.

5. Abelcet was identified as having similar look-alike characteristics to Azilect when scripted. Abelcet is used for the treatment of invasive fungal infections in patients who are refractory to, or intolerant of, conventional Amphotericin B therapy. Both names start with the letter "a" and shares similar ending letters (lcet vs. lect) which contributes to the look-alike similarities between the name pair. However, depending on how the names are scripted, the letter "b" in Abelcet will have an upstroke and the letter "z" in Azilect may have a downstroke which may help to differentiate the two names. Additionally, there are some different product characteristics such as the dosage forms (Azilect is a tablet and Abelcet is an injection), product strengths (0.5 mg and 1 mg tablet vs. 100 mg per 20 mL

suspension for injection) . Additionally, Azilect is prescribed in doses of 0.5 mg or 1 mg while Abelcet is prescribed as 5 mg per kilogram per dose. Thus, the doses would probably not overlap. Although both products are dosed once daily, Abelcet is administered as a two-hour intravenous infusion. Despite some orthographic similarities, the differentiating product characteristics and context of use would help to decrease the potential for confusion between these two products.

abelcet
azilect

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Azilect. In reviewing the proprietary names(s), the primary concerns related to look-alike and/or sound-alike confusion with Azelex and Aricept.

A. Azelex was identified as having similar orthographic and phonetic characteristics with Azilect. Azelex is indicated for the treatment of Acne Vulgaris. These two names may sound-alike when pronounced, particularly if the 'agi' of Azilect and the 'aze' of Azelex are pronounced using the 'asha' sound. The next three letters may also sound similar: 'ele' vs.'ile'. Azelex and Azilect may look-alike when scripted (see below). Each name begins with the letter 'a' and the second letter of both names may have a downstroke (z vs. g) which contributes to look-alike similarities between the two names. Additionally, the middle portion of name (-ele- vs. -ile-) may look similar if the dot above the "i" for Azilect is not prominent or if the letter "e" in Azelex is not written clearly. Differences in product characteristics which may help to distinguish both names include dosage form (tablet vs. topical cream), and route of administration (oral vs. topical). Although, the dosing frequencies (daily vs. twice daily) and strengths are different for the two drugs, postmarketing evidence has shown that confusion may occur when two names look similar with the aforementioned differences. For example, the currently marketed products Visicol and Vesicare have been confused despite differences in strength (1.5 gm vs. 5 mg or 10 mg) and dosing frequency (every 15 minutes vs. once daily) Since Azilect and Azelex are available in a single dosage form, this information may be omitted on a prescription order. Additionally, Azilect is supplied in bottles of 30 tablets while Azelex is available as 30 g and 50 g tubes. It would be possible for a prescription containing the quantity "#30" to be dispensed as a bottle of 30 tablets of Azilect or as a 30 gm tube of Azelex. Postmarketing experience also has shown that practitioners may not be aware of newly marketed products and often dispense an incorrect product due to similarities in spelling with an existing product. Thus in this case, Azelex is a well recognized name and may be inadvertently dispensed for Agilect. Furthermore, topical products such as Azelex are often prescribed with the directions "as directed" (UD). In which case 'UD' could be misinterpreted as 'QD'. Therefore, it would be difficult to differentiate between a prescription for "Azelex UD #30" and "Azilect QD #30" if the strengths is omitted or misinterpreted. Despite the different product characteristics between this name pair, of which some can be omitted, the overwhelming similarities increase the potential for confusion. Therefore, DMETS does not believe that both names should co-exist in the marketplace.

Azelex
Azilect

B. Aricept was identified as having similar look-alike characteristics with Azilect when scripted. Aricept is indicated for mild to moderate dementia of the Alzheimer's type. Both names begin with the letter 'a' and contain four of the same letters 'c, e, i, t' which contributes to the look-alike characteristics between the name pair. However, when scripting, Azilect may have a downstroke with the letter "z" and two upstrokes with the letters "l and t" which may help to differentiate the two names. Aricept, on the other hand only contains one upstroke (the letter "t"). The two names share some product characteristics such as the dosage form (tablet), unit of measure (mg) and dosing frequency (once daily). Although the products are available in different strengths, DMETS notes that the available strengths for both products share the same numerals (5 mg vs .5 mg and 10 mg vs. 1.0 mg,for Aricept and Azilect respectively) which may look similar if the decimal point is overlooked and a trailing zero is present. This creates the potential for misinterpretation and confusion which may lead to medication errors. Orthographic similarities in conjunction with similar product characteristics increase the potential for confusion. Therefore, DMETS does not believe that both names, Aricept and Azilect, should co-exist in the marketplace.

Aricept
Azilect

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/s/

Linda Kim-Jung
5/17/2006 03:09:04 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/17/2006 03:14:27 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/17/2006 03:25:09 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420

FROM:
Division of Neurology, HFD-120
WO, BLDG 22, RM 4344

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 11, 2006		21-641	Proposed Labeling & Trade Name	September 5, 2003 & November 4, 2004 & January 20, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Azilect (rasagiline mesylate) 1 mg Tablets		New Molecular Entity	May 11, 2006

NAME OF FIRM: TEVA PHARMACEUTICALS

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

An earlier consult has been provided, under IND 45,958 , for the review of the propose trade name of AGILECT. An approvable letter was sent on July 2, 2004, and the sponsor replied in a submission dated Nov. 4, 2004. The next action date for this application was August 4, 2005, and another approvable letter issued. This recent submission is dated March 17, 2006 and a 2-month review clock has been determined.

Please review the sponsor's proposal to use the name AZILECT. The sponsor has provided the application electronically, and it can be found in the EDR (\\Cdsesub1\n21641\N_000\

Thank you,
Teresa Wheelous (301) 796-1161

PDUFA DATE: May 17, 2006

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Teresa Wheelous
5/11/2006 10:08:48 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-641 Supplement # Efficacy Supplement Type SE-

Trade Name: Agilect
Established Name: rasagiline mesylate
Strengths: 0.5 mg & 1 mg

Applicant: TEVA Pharmaceutial Industries LTD
Agent for Applicant: J. Michael Nicholas, Ph.D

Date of Application: September 5, 2003
Date of Receipt: September 5, 2003
Date clock started after UN: n/a
Date of Filing Meeting: October 22, 2003
Filing Date: November 4, 2005
Action Goal Date (optional): August 4, 2005 User Fee Goal Date: August 4, 2005

Indication(s) requested: treatment of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(3) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(4) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☐
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☐ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? the entire NDA

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 45,958

- End-of-Phase 2 Meeting(s)? Date(s) June 18, 1997 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) April 20, 2003 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 3, 2005

BACKGROUND: This is a new molecular entity that is currently being evaluated for marketing in several countries throughout the world. Teva currently markets rasagiline in Europe, Israel, and Switzerland under the proprietary name AZILECT®.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Dr. Katz, Dr. Feeney, Dr. Kapcala, Dr. Timmer, Dr. Freed, Dr. Roney, Dr. Jackson, Dr. Yan, Dr. Racoosin, CDR Wheelous

ASSIGNED REVIEWERS (including those not present at filing meeting) : ,

Discipline	**Reviewer**
Medical:	Kapcala
Secondary Medical:	Jones
Statistical:	Yan
Pharmacology:	Roney
Statistical Pharmacology:	Massie
Chemistry:	Timmer
Environmental Assessment (if needed):	
Biopharmaceutical:	Jackson
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Khin
Regulatory Project Management:	Wheelous
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: entire NDA submitted electronically

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

CDR Teresa Wheelous
Regulatory Project Manager, HFD-120

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☒

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☒

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   ***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES ☐ NO ☒

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☒

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
  YES ☐ NO ☒

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
  N/A ☒ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
  N/A ☒ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# 45958 NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☐ NO ☐

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

/s/

Teresa Wheelous
5/9/2006 09:10:40 AM
CSO

Wheelous, Teresa A

From: Wheelous, Teresa A
nt: Wednesday, May 03, 2006 11:37 AM
o: 'Dennis.Williams@tevaneuro.com'
Subject: NDA 21-641 Rasagiline Draft Labeling

Attachments: Division Proposed Labeling to sponsor 050306.doc

Dennis,

The attached labeling is a starting point for labeling negotiations regarding NDA 21-641 Rasagiline. This labeling (1) uses the base document sent to you in the first action letter, (2) this draft labeling has not been vetted thru all of the review disciplines so additional revisions should be expected, and (3) the Melanoma section of this labeling is a place holder and will be changed after future internal discussions.

Division Proposed Labeling to ...

Regards,
CDR Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
FDA
Division of Neurology
10903 New Hampshire Avenue, Bldg. #22
Silver Spring, MD 20993-0002
(telephone) 301-796-1161
(fax) 301-796-9842
New email address: teresa.wheelous@fda.hhs.gov

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.
Sr. Director, U.S. Regulatory Affairs
425 Privet Road
Horsham, PA 19044-8005

Dear Dr. Nicholas:

We acknowledge receipt on March 17, 2006 of your March 17, 2006 resubmission to your new drug application for Azilect (rasagiline mesylate) 1 mg Tablet.

We consider this a complete, class 1 response to our August 4, 2005, action letter. Therefore, the user fee goal date is **May 17, 2006**.

If you have any question, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
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/

Russell Katz
4/20/2006 08:00:40 AM

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.
Sr. Director, U.S. Regulatory Affairs
425 Privet Road
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 on January 20, 2006, of your January 20, 2006, submission to your new drug application (NDA) for (rasagiline mesylate) 1 mg Tablet.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. Listed below are 3 requests for additional studies taken verbatim from our Approvable Letter to you. In your response to the Approvable Letter we expected that these studies would have been performed or, alternatively, that you would have provided arguments that the data were not critical to an Approval Action. You have not provided such arguments. We note that you have concluded *"that there are no safety concerns that would preclude this trial from being conducted post approval"* for each of the 3 pharmacokinetic (PK) studies requested. We believe that you have concluded that because you have agreed to include language in product labeling that advises patients that they should restrict their dietary intake of tyramine containing foods, the requested studies need not be submitted prior to approval. We do not agree that the necessity to perform these studies is linked solely to the setting in which patients receive an unrestricted diet. Indeed, we believe that the data derived from these studies have important safety implications related to all safety issues independent of tyramine sensitivity. Therefore, we believe these issues must still be addressed.

Clinical Pharmacology & Biopharmaceutics

> *"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."*

"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: 1mg, 2 mg, and 6 mg)."

"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)."

You should conduct these three studies characterizing these effects prior to approval or provide a compelling argument why it is not necessary to complete them prior to approval and why it should be acceptable to provide any of these data post-approval as a phase 4 commitment. We have the following additional comments, both bearing on phase 4 commitments.

Clinical

We note that since we issued the approvable letter an important ICH Guidance ("E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs") has recently (October 2005) been issued. This guidance deals with conducting a "thorough" QTc study to characterize effects of a drug on cardiac repolarization. We provide you with a quotation from the scope section of this guidance.

"The recommendations contained in this document are generally applicable to new drugs having systemic bioavailability, but may not apply to products with highly localized distribution and those administered topically and not absorbed. The focus is on agents being developed for uses other than the control of arrhythmias, as antiarrhythmic drugs can prolong the QT/QTc interval as a part of their mechanism of clinical efficacy. While this document is concerned primarily with the development of novel agents, the recommendations might also be applicable to approved drugs when a new dose or route of administration is being developed that results in significantly higher exposure (i.e., C_{max} or AUC)."

Since we issued the last approvable letter we have concluded that it is important and necessary that you conduct a "thorough" QTc study characterizing the effects of rasagiline on cardiac repolarization in humans. This "thorough" QTc study can be conducted post-approval as a phase 4 commitment. Please indicate in your response your commitment to conduct a "thorough" QTc study as a phase 4 commitment and the necessary dates related to fulfilling this phase 4 commitment.

Nonclinical

You have committed to conduct a repeat oral embryo-fetal development study in rabbit. According to the protocol provided in your January 20, 2006, submission, this study has been completed and an audited draft report will be available on March 2, 2006. Please confirm these dates and provide a date by which a final report will be submitted to the Agency.

If you have any question, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
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/

Russell Katz
2/15/2006 09:58:33 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 7, 2005

TIME: 11 AM – 12 Noon

LOCATION: WO Bldg. #22, Conference Room 1419

APPLICATION: NDA 21-641 Rasagiline

TYPE OF MEETING: End of Review

MEETING CHAIR: Dr. Temple

FDA ATTENDEES, TITLES, AND DIVISION
Dr. Robert Temple – Office Director, ODE 1
Dr. Russell Katz – Division Director, HFD-120
Dr. John Feeney – Group Leader, HFD-120
Dr. Judith Racoosin – Safety Team Leader, HFD-120
Dr. Lisa Jones – Safety Reviewer, HFD-120
Dr. Paul Roney – Pharmacology & Toxicology Reviewer
Dr. Lois Freed – Pharmacology & Toxicology Supervisor
CDR Teresa Wheelous – Sr. Regulatory Management Officer, HFD-120

TEVA Pharmaceutical Industries, LTD ATTENDEES AND TITLES:
Teva Neuroscience
Rivka Kreitman, Ph.D, Vice President, Innovative Research and Development
J. Michael Nicholas, Ph.D., Senior Director of Regulatory Affairs
Dennis Williams, R.Ph, Sr. Manager, Regulatory Affairs

Teva Israel
Michal Herskovitz, ChemEng, Senior Director, Global Regulatory Affairs
Ruth Levy, Ph.D., Executive Director, Global Pipeline Development
Noa Leibovitch, Ph.D., Associate Director, Global Pipeline Development
Yael Keenan, Ph.D., Associate Director, Global Clinical Research
Galia Shifroni
John Ienni
Tami Yardeni

External Consultants

Darrell Rigel, M.D., Clinical Professor of Dermatology, NYU Medical Center

BACKGROUND AND MEETING OBJECTIVES:

The purpose of the meeting is to discuss the melanoma issues raised in the August 4, 2005 approvable letter.

DISCUSSION POINTS:

- The Teva representatives commenced by stating that their goal for the meeting was to answer any remaining FDA questions regarding rasagiline and melanoma. Teva then reviewed their responses (sent via e-mail December 7, 2005 [the morning of the meeting]) to a series of previous FDA questions on the meeting briefing material (see Appendix). As a follow-up to a question regarding the effect of discontinuing subjects on melanoma rates by duration of exposure, Teva stated that subjects who did and did not discontinue had similar melanoma risk factors.

- In a discussion of the dose-response analysis, the merits and limitations of different methods for ascertaining subject dose (i.e. modal, highest dose, etc.) were reviewed. Dr. Katz stated that it was his understanding that the modal dose represented all or the large majority of a subject's exposure in most cases. Dr. — stated that Teva had also performed a dose-response analysis by cumulative dose, which the FDA had not yet seen. Teva then shared the results of the cumulative dose analysis. The results were not dissimilar from other dose analyses that have been conducted (e.g. the highest rate was in the lowest cumulative dose category, the lowest rate was in the second lowest cumulative dose category, with rising rates over subsequent higher cumulative dose categories).

- Dr. Feeney asked the Teva representatives for their thoughts on the FDA comparison of the sponsor's EP002 cohort study and the American Academy of Dermatology (AAD) melanoma screening data, as Teva had not addressed this analysis in their meeting briefing materials. Teva stated that there was insufficient time before the meeting for a full evaluation, but that the comparison appeared to be supportive of a relationship between Parkinson's disease and melanoma. Dr. Rigel noted that he was involved in the AAD screening program and that approximately 20% of subjects had more than one screening, which differed from the population in the EP002 study.

- Regarding a Phase IV, large simple trial, Teva stated that performing a placebo-controlled study would be difficult. Dr. Temple asked why this was so, and Teva stated that physicians are less likely to enroll patients in placebo-controlled studies. Dr. Temple noted that, except for rasagiline, the proposed study would allow subjects to follow whatever treatment regimen their physician recommended. Dr. Temple believed physician reluctance to enroll patients would be reduced if this was clearly communicated. Teva stated that study planning was ongoing.

- Dr. — stated that the FDA's comparison of the melanoma rate in the rasagiline development program to the melanoma rate in other Parkinson's disease (PD) development programs was confounded by the dermatologic examinations in the rasagiline development program. Dr. Katz noted that when the comparison was limited to only the melanomas diagnosed prior to the screening program, rasagiline still had a higher rate than other PD development programs. Dr. — stated that three of the six pre-screening melanomas

should arguably not be included as cases, reportedly because one of the cases was diagnosed very early during rasagiline treatment (and thus assumed to be a preexisting lesion), and the other two were reported after a "Dear Healthcare Provider" letter was sent to investigators describing the melanoma cases in the development program (we are waiting on confirmation from the sponsor that these were their reasons for excluding the three cases).

- The Division agreed to provide Teva with a list of follow-up questions resulting from discussion at the meeting. These questions were sent on December 9, 2005. These questions follow below:

1. Please submit an analysis comparing melanoma risk factors and other melanoma-relevant demographic factors (notably, age and sex) for the cohorts of continuing and discontinuing subjects in TEMPO and PRESTO (for each study separately). For TEMPO, in particular, another melanoma-relevant factor that should be compared for the continuation and discontinuation cohorts is the addition of L-dopa therapy

Due to screening initiation and other melanoma awareness activities, the comparison should be performed at various time points, assessed as both time from study start (for example, at six months, 12 months, 24 months, 36 months) and time by calendar year (for example, all subjects, regardless of time in study, before and after commencement of dermatologic screening.)

2. In the briefing packet, you noted that several programming errors affected some of the results previously provided (pg. 6). Please provide a version of Table 19 below using the corrected data. You should have already received this table as part of the shared FDA melanoma review, but it is also included below for your convenience.

FDA Table 19 (pg. 35): Number and Risk of Melanomas in the Immediate and Delayed Start Groups by Time Strata from Time of *First Study Dose (Placebo or Rasagiline)*

Number of Melanomas Per Treatment Group	**0-6 Months**	**6 –12 Months**	**12-18 Months**	**18-24 Months**	**>24 Months**
PRESTO Immediate	3 (1%)	2 (0.6%)	1 (0.3%)	0	0
PRESTO Delayed	0	0	1 (0.6%)	0	0
TEMPO Immediate	1 (0.4%)	0	2	0	6 (2%)
TEMPO Delayed	0	0	0	0	1 (0.7%)
Total Immediate	**3 (0.5%)**	**2 (0.3%)**	**3 (0.5%)**	**0**	**6 (1%)**
Total Delayed	**1 (0.3%)**	**0**	**1 (0.3%)**	**0**	**1 (0.3%)**

3. Regarding the number of melanoma cases which should be included in the pre-screening melanoma rate calculation:

(a) The briefing packet noted that there were six melanomas (4 in situ and 2 invasive) identified prior to initiation of mandatory dermatological screening (pg. 11). At the meeting there was discussion that the more appropriate case count is three melanomas. Assuming that you would exclude the advanced melanoma occurring two months after study initiation, which other melanoma cases do you believe should not be included among the six pre-screening cases

(i.e., which other two cases occurred after the "Dear Investigator" letter and before screening began?)

(b) To clarify, were there melanoma awareness measures (the "Dear Investigator" letter along with the Investigator Brochure) prior to the initiation of screening? What were the approximate dates for these measures and the initiation of screening? Is there any evidence that the pre-screening melanoma awareness activities resulted in heightened melanoma detection?

4. At the meeting, a dose-response analysis using cumulative dose was shown. Please provide us with the results of this analysis (including confidence intervals for the point estimates).

An additional note regarding the safety update:
Within the section on patient discontinuation, for patients who discontinued for reasons of "physician decision" or "patient decision", please examine the case report form and any other available information for underlying reasons for discontinuation (and include that information, where identified).

Appendix: Teva Responses to DNP Questions on the Pre-Meeting Briefing Package

1. In the Dose-Response analysis, which cases were included in the "0 mg" group? Were cases of melanoma found prior to treatment initiation included? As the purpose of the analysis is to examine treatment-emergent cases, only cases in subjects actually treated with placebo should be included in the "0 mg" group.

Response: Only placebo case (treatment emergent) in the LARGO study is included. This is patient number 41604 in attachment 2 of the briefing book.

2. In the Dose-Response analysis, how was the person-time (denominator) distributed among the various doses the subjects were exposed to? For example, if a patient was treated with 0.5 mg initially and then later increased to 1 mg, was the time they were treated with each dose allotted to that dose?

Response: actual dose was allocated to each dose. In the above example, this patient attributes exposure to both doses proportionally to time spent on applicable dose.

3. Could a copy of Figure 1 (pg. 8) with the number of cases and person-time included be provided?

Response: Post-Text tables 2, 3, 4 in the briefing book provide the number of cases and person-time.

4. On page 10 (Delayed vs. Immediate Start Analysis), it is stated that "Comparison of each time strata from initial rasagiline start...demonstrates that CIs for immediate and delayed starters have a substantial overlapping and the p values are insignificant." Which time strata are referred to in this statement?

Response: The CI of incidence rates between Presto immediate and Presto delayed, Tempo immediate and Tempo delayed, and total immediate and total delayed in any time point overlap as presented in post text tables 9 and 10 of briefing book.

5. Given that the rate of melanoma over time is affected by dropouts, did you do any melanoma surveillance of subjects who discontinued from the rasagiline open extension studies?

Response: Subjects who discontinued the open extension studies did not have followup examinations.

6. Your submission stated that you would investigate the feasibility of the phase IV trial design and provide additional information in advance of the meeting. Are there additional pre-meeting details on the melanoma Phase IV study design?

Response: We are still investigating the feasibility of trial designs. A synopsis for a randomized large simple trial is attached.

A

7 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/

Russell Katz
2/7/2006 03:27:35 PM

B

10 Page(s) Withheld

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

__✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Wheelous, Teresa A

·om: Dennis.Williams@tevaneuro.com
ɹnt: Tuesday, May 10, 2005 4:11 PM
To: Wheelous, Teresa A
Subject: Re: Safety Question for Rasagiline

MM graphs.doc (31 KB)

Hi Teresa,

Attached below is the requested graph.

(See attached file: MM graphs.doc)

Regards,
Dennis

"Wheelous, Teresa A" <WHEELOUST@cder.fda.gov>
05/05/2005 05:37 PM

To: "'Dennis.Williams@tevaneuro.com'" <Dennis.Williams@tevaneuro.com>
cc:
Subject: Safety Question for Rasagiline

Dennis,

This is another safety question it's in regards to the same thing I e-mailed you about the other day.

Regarding the request for the updated melanoma-time epoch described below, please also include confidence intervals for the various time strata.

In the ISS of the rasagiline NDA (Appendix 18.3, Figure 2), a bar-graph figure was prepared demonstrating the number of melanoma cases per 100 patient-years of exposure for consecutive time periods (0-0.5 years, 0.5-1 year, 1-2 years, etc). The FDA reviewer subsequently asked that this figure be recalculated with each subject contributing time to the various strata they passed through during their total time in the study (for example, a subject who remained in the study for 1.5 years would contribute 0.5 years to the first six-month strata, 0.5 years to the second six-month strata, and 0.5 years to the 1-2 year rata). It is now requested that this figure be updated to include information on lanoma and subject exposure up until the time of the most recent datalock. As per the preceding, please distribute person-time among the various time strata each subject passes through, and not only to the time period of their complete exposure (as was done in the initial figure construction.)

Thanks,
Teresa

MEMORANDUM OF TELECON

DATE: May 9, 2005

APPLICATION NUMBER: NDA 21-641 Rasagiline

BETWEEN:
Phone: 1-888-279-8822

TEVA Pharmaceuticals
Dennis Williams - Sr. Manager, Regulatory Affairs

FDA
Dr. John Feeney – Group Leader
Dr. Lois Freed – Pharmacology / Toxicology Team Leader
Dr. Tristan Massie – Biometrics Reviewer
CDR Teresa Wheelous – Sr. Regulatory Management Officer

SUBJECT: Correction to Electronic Dataset for the Rat Carcinogenicity Study Needed
BACKGROUND:
The Sponsor requested a teleconference to further discuss the Division's continuing concerns regarding problems with the electronic dataset for the rat carcinogenicity study. (A previous telecon was held on April 5, 2005 during which the Division initially discussed with the Sponsor the problems encountered with this electronic dataset.) The most recent electronic dataset submitted by the Sponsor (04/28/05) presents the same problem as the electronic dataset submitted in the Sponsor's initial response to the Agency's Approvable letter (07/02/04).

DISCUSSION:
Specifically, there is disagreement between the MICRO and TUMOR data sets for certain tissues on how many terminally sacrificed animals were examined for tumor incidence. The Division reiterated that the carcinogenicity software used by the Agency relies solely on the TUMOR data set; however, there is concern regarding it's validity since it has certain organ examination records that are not consistent with those in the MICRO data set. For example, the TUMOR data set suggests that thyroid gland was examined in only 6 mid-dose males that were terminally sacrificed. However, 23 mid-dose males were killed at terminal sacrifice, and the MICRO dataset suggests that the thyroid gland was examined in all 23 of these animals. A similar problem occurs for other tissues. The result of these discrepancies is that there are statistically significant tumor findings based on the TUMOR.XPT file that are not significant based on the MICRO.xpt file.

The Division indicated that the TUMOR.XPT file needs to be corrected. The Sponsor stated that they now understand the problem and will correct it; however, there needs to be an internal discussion before the Sponsor can provide an estimate of how long this will take.

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

/s/

Teresa Wheelous
6/2/05 11:33:28 AM
CSO

Lois Freed
6/11/05 07:23:36 AM
PHARMACOLOGIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-641

TEVA Pharmaceuticals, Inc.
Attention: J. Michaels Nicholas, Ph.D.
U.S. Regulatory Affairs and Pharmacovigilance
425 Privet Road
Horsham, PA 19044-8005

Dear Dr. Nicholas:

Please refer to your November 4, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (rasagiline) 1 mg tablet.

On April 29, 2005, we received your April 28, 2005 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 4, 2005.

If you have any questions, call me at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
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/

Russell Katz
5/3/05 09:28:51 AM

Wheelous, Teresa A

From: Dennis.Williams@tevaneuro.com
Sent: Friday, May 06, 2005 2:27 PM
To: Wheelous, Teresa A
Subject: Re: Safety Question for Rasagiline

Hi Teresa,

Attached is the dial in numbers for the telecon on Monday at 10:15.

1-888-279-8822

Who will participate from your side?

Is there any way for the statistical reviewer to send something in advance of the meeting to help us understand the problem? We have had an independent stat review of the data since the question on Monday and were not able to identify any problems in the dataset.

Regards,
Dennis

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: "Wheelous, Teresa A" [WHEELOUST@cder.fda.gov]
Sent: 05/05/2005 05:37 PM
To: Dennis Williams
Subject: Safety Question for Rasagiline

Dennis,

This is another safety question it's in regards to the same thing I e-mailed you about the other day.

Regarding the request for the updated melanoma-time epoch described below, please also include confidence intervals for the various time strata.

In the ISS of the rasagiline NDA (Appendix 18.3, Figure 2), a bar-graph figure was prepared demonstrating the number of melanoma cases per 100 patient-years of exposure for consecutive time periods (0-0.5 years, 0.5-1 year, 1-2 years, etc). The FDA reviewer subsequently asked that this figure be recalculated with each subject contributing time to the

various strata they passed through during their total time in the study (for example, a subject who remained in the study for 1.5 years would contribute 0.5 years to the first six-month strata, 0.5 years to the second six-month strata, and 0.5 years to the 1-2 year strata). It is now requested that this figure be updated to include information on melanoma and subject exposure up until the time of the most recent datalock. As per the preceding, please distribute person-time among the various time strata each subject passes through, and not only to the time period of their complete exposure (as was done in the initial figure construction.)

Thanks,
Teresa

Wheelous, Teresa A

om: Dennis.Williams@tevaneuro.com
ent: Wednesday, May 04, 2005 1:44 PM
To: Wheelous, Teresa A
Subject: Re: Safety Question for Rasagiline

Hi Teresa,

I believe this response will be ready tomorrow, but I will confirm and get back to you.

Regards,
Dennis

"Wheelous, Teresa A" <WHEELOUST@cder.fda.gov>
05/04/2005 01:19 PM

To: "'Dennis.Williams@tevaneuro.com'" <Dennis.Williams@tevaneuro.com>
cc:
Subject: Safety Question for Rasagiline

Dennis,

The safety reviewer would like to know when we might receive a response to the following question:

Question for Teva:

In the ISS of the rasagiline NDA (Appendix 18.3, Figure 2), a bar-graph figure was prepared demonstrating the number of melanoma cases per 100 patient-years of exposure for consecutive time periods (0-0.5 years, 0.5-1 year, 1-2 years, etc). The FDA reviewer subsequently asked that this figure be recalculated with each subject contributing time to the various strata they passed through during their total time in the study (for example, a subject who remained in the study for 1.5 years would contribute 0.5 years to the first six-month strata, 0.5 years to the second six-month strata, and 0.5 years to the 1-2 year strata). It is now requested that this figure be updated to include information on melanoma and subject exposure up until the time of the most recent datalock. As per the preceding, please distribute person-time among the various time strata each subject passes through, and not only to the time period of their complete exposure (as was done in the initial figure construction.)

Thank you,
Teresa

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Tuesday, May 03, 2005 8:50 AM
To: 'Dennis.Williams@tevaneuro.com'
Subject: RE: NDA 21-641 Carcinogenicity data

Dennis,

The Stat reviewer has a request for further clarification on the rat carcinogenicity data submission:

In the MICRO.xpt file submitted on April 28 it appears that all 65 animals in each group are accounted for with tissues categorized as being either "Abnormal", "Except'n", or "Normal". However, in the TUMOR.xpt file the data suggest that not all tissues of the terminally killed male middle dose group were examined. If they were examined why does the number at risk during terminal sacrifice not correspond to the number killed? This only seems to be a problem for the male middle dose (1mg/kg) group. For example, the TUMOR data set suggests that there were 6 male middle dose animals who had their thyroid examined after terminal sacrifice. However, 23 male middle dose animals were killed during TS. There are other tissues with similar inconsistencies. Please clarify this issue for all tissues of the male rats as our carcinogenicity software relies on the TUMOR.xpt data set and we need to know that it is accurate.

-----Original Message-----
From: Dennis.Williams@tevaneuro.com [mailto:Dennis.Williams@tevaneuro.com]
Sent: Monday, May 02, 2005 10:46 AM
To: Wheelous, Teresa A
Subject: RE: NDA 21-641 Carcinogenicity data

Teresa,

Are these comments expected today?

There is a reason I am trying to determine if the Division will make a decision today. Tomorrow is the date that Teva releases its 1st quarter results to the financial community. There is a Q & A session that follows that investors can ask the CEO questions. It is likely that someone will ask if Teva still expects an action letter on May 4, 2005. Based on recent events regarding the SAS issue, it is not clear exactly how to answer this question should it arise. For that reason, I just trying to follow-up so I will have the most up to date information available.

Regards,
Dennis

"Wheelous, Teresa A" <WHEELOUST@cder.fda.gov> — To: "'Dennis.Williams@tevaneuro.com'" <Dennis.Williams@tevaneuro.com> — cc: — Subject: RE: NDA 21-641 Carcinogenicity data — 05/02/2005 10:35 AM

Dennis,

we are waiting for comments from the reviewer before a decision can be made.

Teresa

-----Original Message-----
From: Dennis.Williams@tevaneuro.com [mailto:Dennis.Williams@tevaneuro.com]
Sent: Monday, May 02, 2005 10:34 AM
To: Wheelous, Teresa A
Subject: RE: NDA 21-641 Carcinogenicity data

Hi Teresa,

I wanted to follow-up with you regarding the submission of the SAS datasets. Do you think the Division will make a decision whether to extend the clock or not today?

Regards,
Dennis

"Wheelous, Teresa A" <WHEELOUST@cder.fda.gov>

04/29/2005 03:34 PM

To: Dennis.Williams@tevaneuro.com' <Dennis.Williams@tevaneuro.com>

cc:

Subject: RE: NDA 21-641 Carcinogenicity data

Dennis,

Yes, please send the datasets via email. The reviewer would like to look at the datasets as soon as possible.

Teresa

-----Original Message-----
From: Dennis.Williams@tevaneuro.com [mailto:Dennis.Williams@tevaneuro.com]
Sent: Friday, April 29, 2005 2:24 PM
To: Wheelous, Teresa A
Subject: RE: NDA 21-641 Carcinogenicity data

Hi Teresa

T will send in the SX submission with protocol and send desk copies.

Based on the fact the reviewer will conduct a cursory review, do you want me to send you the SAS datsets in e-mail to expedite this review?

Regards,
Dennis

"Wheelous, Teresa A" <WHEELOUST@cder.fda.gov>

04/29/2005 02:04 PM

To: "'Dennis.Williams@tevaneuro.com'" <Dennis.Williams@tevaneuro.com>

cc:

Subject: RE: NDA 21-641 Carcinogenicity data

Dennis,

Once the reviewer has had an opportunity to conduct a cursory review of the content of the submission, a decision will be made whether or not to extend the clock.

As for the special protocol (SX) submission, please include the protocol with the special protocol assessment. Also, please send me four desk copies of the SX submission (with protocol).

Thank you

Teresa

-----Original Message-----
From: Dennis.Williams@tevaneuro.com [mailto:Dennis.Williams@tevaneuro.com]
Sent: Friday, April 29, 2005 1:58 PM
To: Wheelous, Teresa A
Subject: RE: NDA 21-641 Carcinogenicity data

Teresa,

'll Teva receive official notification on an extension of the action date or is that .cision not final?

Additionally, with regard to a voicemail message I left you yesterday, a request for special protocol assessment was submitted yesterday (Document room received today) with regard to new Disease Modification Protocol for Parkinson's Disease (IND 45,958). This

protocol was submitted on April 11, 2005 (serial 226). I submitted the request for special protocol assessment without sending the same protocol again. If you need additional copies of the Protocol (or electronic copies) please let me know.

Regards,
Dennis

"Wheelous, Teresa A" <WHEELOUST@cder.fda.gov>

To: "'Dennis.Williams@tevaneuro.com'" <Dennis.Williams@tevaneuro.com>

cc:

Subject: RE: NDA 21-641 Carcinogenicity data

04/29/2005 01:42 PM

Dennis,

Thank you for the notification.

Teresa

-----Original Message-----
From: Dennis.Williams@tevaneuro.com [mailto:Dennis.Williams@tevaneuro.com]
Sent: Friday, April 29, 2005 1:34 PM
To: WHEELOUST@cder.fda.gov
Subject: NDA 21-641 Carcinogenicity data

Hello Teresa,

The SAS datasets for study 6751-109 were submitted yesterday. I have verified with the CDER staff in the central document room that the submission has been received.

Since I do not know how long it takes to load e-submissions to the Electronic Document Room, I would be happy to e-mail you this submission if you would like. The SAS datasets are relatively small (15 MB).

Regards,
Dennis

This message is intended solely for the designated recipient(s). It may contain confidential or proprietary information and may be subject to attorney-client privilege or other confidentiality protections. If you are not a designated recipient you may not review, copy or distribute this message. If you receive this in error, please notify the sender by reply e-mail and delete this message. Thank you.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-641

TEVA Pharmaceuticals, Inc.
Attention: J. Michaels Nicholas, Ph.D.
U.S. Regulatory Affairs and Pharmacovigilance
425 Privet Road
Horsham, PA 19044-8005

Dear Dr. Nicholas:

Please refer to your November 4, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (rasagiline) 1 mg tablet.

On April 29, 2005, we received your April 28, 2005 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 4, 2005.

If you have any questions, call me at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
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/

Russell Katz
5/3/05 09:28:51 AM

Wheelous, Teresa A

om: Wheelous, Teresa A
ent: Wednesday, April 20, 2005 12:53 PM
To: 'Dennis.Williams@tevaneuro.com'
Subject: Rasagiline Melanoma Safety Request

Dennis,

The safety reviewer has the following melanoma request:

In the ISS of the rasagiline NDA (Appendix 18.3, Figure 2), a bar-graph figure was prepared demonstrating the number of melanoma cases per 100 patient-years of exposure for consecutive time periods (0-0.5 years, 0.5-1 year, 1-2 years, etc). The FDA reviewer subsequently asked that this figure be recalculated with each subject contributing time to the various strata they passed through during their total time in the study (for example, a subject who remained in the study for 1.5 years would contribute 0.5 years to the first six-month strata, 0.5 years to the second six-month strata, and 0.5 years to the 1-2 year strata). It is now requested that this figure be updated to include information on melanoma and subject exposure up until the time of the most recent datalock. As per the preceding, please distribute person-time among the various time strata each subject passes through, and not only to the time period of their complete exposure (as was done in the initial figure construction.)

Thank you,

CDR Teresa Wheelous, R. Ph.
Senior Regulatory Management Officer
Office of Drug Evaluation I
vision of Neuropharmacological Drug Products
HFD-120
1451 Rockville Pike
Rockville, MD 20852
Telephone (301) 594-2850
Fax (301) 594-2859

Wheelous, Teresa A

om: Wheelous, Teresa A
ent: Friday, April 15, 2005 2:36 PM
To: 'Dennis.Williams@tevaneuro.com'
Subject: Melanoma Follow-up Questions

Dennis,

The safety reviewer has the following melanoma questions:

Regarding the reading of the melanoma screening biopsies in the local and central laboratories within the rasagiline development program:

1. What was the training of the persons reading the biopsies in both the local and central laboratories? Specifically, was the final diagnosis (in both the local and central labs) made by a dermatopathologist or a general pathologist?

2. Were any special stains or techniques, beyond H&E staining, used in the diagnoses of melanomas versus nevi?

3. Could a brief summary be provided, similar to that provided for the few discrepant readings of melanomas versus nevi between the local and central laboratories, for any discrepancies for invasive ersus in situ melanomas?

Thank you,

CDR Teresa Wheelous, R. Ph.
Senior Regulatory Management Officer
Office of Drug Evaluation I
Division of Neuropharmacological Drug Products
HFD-120
1451 Rockville Pike
Rockville, MD 20852
Telephone (301) 594-2850
Fax (301) 594-2859

Wheelous, Teresa A

om: Wheelous, Teresa A
ent: Thursday, April 07, 2005 2:10 PM
To: 'Dennis.Williams@tevaneuro.com'
Subject: Rasagiline Safety Information Request

Dennis,

The following are Safety QUESTIONS FOR TEVA:

1. On pg. 29, Section 2.1.1 of the Response to Approvable Letter Safety Update (ISS), it is stated that: "A total of 1991 subjects who participated in the rasagiline clinical development program are currently included in the database. Of these, 1584 subjects including PD and AD patients and healthy volunteers were exposed to rasagiline for a totoal of 2375 subject years."

Were the 1584 subjects those in multi-dose studies, and hence contributing to person-time exposure? The purpose of this question is to clarify the status of the 407 subjects who make up the difference between the 1991 total subjects and the 1584 for whom person-year exposure was tallied.

2. Regarding Section 5.5.1(Deaths) on pg. 56 of the ISS (Response to Approvable Letter), interpretation of these pooled mortality risks and rates is complicated by the fact that such pooling combines rasagiline monotherapy and adjunctive therapy trials. Mortality rates in the untreated early and advanced PD populations differ substantially, so one would expect those differences to be reflected in the rates described above. Since an entacapone arm was only included in adjunctive studies, it is not unexpected that the mortality rate in that group is higher than the rasagiline rate which combines early and advanced PD patient trials.

It would be more useful to look at the comparative mortality risk and rates (by treatment group) within Cohort 1 (monotherapy) and Cohort 2 (adjunctive therapy) cohorts. Please provide this.

3. In the ISS/Safety Update for the Response to Approvable Letter, pg. 62, it is stated that: "Five patients who had discontinuation reason 'due to AE' did not have any AE marked with 'dose stopped.' Are these five included among the subjects addressed in the "Increased Attribution of Discontinuations to A Specific Adverse Event" section of the Response to Approvable Letter? If not, is it possible to determine the adverse event leading to discontinuation?

4. In Table 6, Response to Approvable Letter: Melanoma, pg. 8 ("Delayed-Start") analysis, can the table be reconfigured to contain the number of subjects in each cell as well as the person-year exposures? The number of subjects should be considered the number entering each of the study phases (ie. placebo-controlled, active treatment and open label).

5. On pg. 21 of the EP002 Final Study Report, 120 Day Safety Update, it is stated that "The 2-year historical period used in this analysis was determined a priori (see Protocol EP002, Appendix 15.1.1) based on the ease of obtaining appropriate documentation fo the past melanoma cases." Was medical record verification obtained for the past melanomas reported by the subjects?

6. Were the pathologists in both the local and central laboratories who examined the biopsies from the dermatologic screening blinded to subject treatment group?

7. For ECG parameter changes calculated as change from baseline to Last Observed Value (LOV) (as in Table 1, QTc Mean Interval Descriptive Statistics of Change from Screening to Last Observed Value for Monotherapy Study TEMPO, pg. 7), can the table and related data be re-calculated as change from baseline to Maximal Observed Value?

Also, the TEMPO study report (pg. 60) states "ECG was carried out at screening, Week 14, termination of the placebo-controlled phase (Week 26), study drug discontinuation (Week 52) and at follow-up Visit (Week 58)." Were subjects still receiving treatment with rasagiline at the time of the LOV ECG, and if not how long had they been untreated?

8. On pg. 5 of the Response to Approvable Letter: Blood Pressure, the statement is made: "None of the decreases in nding BP manifested clinically." Could you please expand upon what is meant by "manifested clinically": that the subjects were asymptomatic? Does this mean that no adverse events were reported?

9. In Cohort Study EP002, is it possible to calculate the risk of melanoma in subjects with and without levodopa treatment? We appreciate that since the majority of subjects were receiving with levodopa this is not an ideal comparison.

Please limit the calculation to those melanomas diagnosed during the dermatologic screening exam, and not those diagnosed in the two-years prior to study enrollment.

Thanks,
Teresa Wheelous

Appears This Way
On Original

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Wednesday, April 06, 2005 3:59 PM
To: 'Dennis.Williams@tevaneuro.com'
Subject: Rasagiline NDA 21-641 Clin Pharm Reply to Nov. 18, 2004 Submission

Dennis,

THE FOLLOWING COMMENTS WERE FAXED TO THE FIRM October 27, 2004:

QUESTION:
1. You should do a formal log dose regression on the tyramine study P94159 to clearly establish if the PK is indeed nonlinear for AUC between the 1 mg and 2 mg.

2. You should present detailed calculations showing the individual data for all pharmacokinetic calculations in Appendix 2 Tables 1 and 2. These tables should be
annotated for easy identification with their EDR origin or the original tables can be presented in proximity to the newly calculated mean values.

3. You should make pharmacokinetic comparisons only to subjects whom exhibit the same pharmacokinetics. For example, males in study CD596 (1-20 mg) exhibit nonlinear pharmacokinetics following single dosing, but linear kinetics after multiple dosing (2-10 mg/day). However in study P94159 at multiple doses of 1 mg and 2 mg/day, the pharmacokinetics appears to be nonlinear on Day 9. Therefore it would not be meaningful to compare the multiple dose data from studies CD596 and P94159. This principle should be followed in all of your comparisons across treatment groups.

The following are Clinical Pharmacology & Biopharmaceutics responses to your Nov. 18, 2004 submission to NDA 21641 Rasagiline in which you respond to three recommendations provided in the Oct. 27, 2004 facsimile referenced above :

FDA Reply - Question #1:
The following table for rasagiline analysis for study P94159 was submitted in the original application.
Parameter Rasagiline Aminoindan
Method GC\MS GC\MS
Sensitivity/LOQ 0.25 ng/ml 0.5 ng/ml
Linearity (Standard curve
samples)
0.25-10 ng/ml 0.5-10 ng/ml
Quality Control (QC)
Samples
0.4 ng/ml
2.50 ng/ml
7.5 ng/ml
0.75 ng/ml
2.50 ng/ml
7.5 ng/ml
Precision of Standards
(%CV)
3.7%@0.25ng/ml
2.50%@10.0 ng/ml
6.14% @ 0.5 ng/ml
2.67% @ 10 ng/ml

Precision of QC Samples
(%CV)
9.8 @ 0.4 ng/ml
52 @ 7.5 ng/ml
5.05% @ 0.75 ng/ml
4.56% @ 7.5 ng/ml
Accuracy of Standards (%) 93%@ 0.25ng/ml
99.3%@ 10ng/ml
99.3% @ 0.5 ng/ml
99.0% @ 10 ng/ml
Accuracy of QC Samples (%) 99% @ 0.4 ng/ml
99% @ 7.5 ng/ml
99% @ 0.75 ng/ml
103% @ 7.5 ng/ml

This table indicates that your assay was reliable, however you are currently stating that "The plasma levels following 1 mg rasagiline dose are very low and the constraints of the bioanalytical limits of quantitation of PAI are preventing an accurate estimation of exposure at the relevant clinical dose." You need to explain what you mean by "The plasma levels following 1 mg rasagiline dose are very low and the assay not being accurate." Is the problem related to stability, assay sensitivity, recovery etc. You must be very clear since this is pivotal information for all studies at the 1 mg dose.

Further, there were several studies, P94159, CC547, CC596, TVP-1012/424, TVP-1012/425, TVP-1012/426, TVP-1012/430, TVP-1012/112, TVP-1012/132, and TVP-1012/231 where a 1 mg dose was studied either under single or multiple dose conditions. Based upon your claimed assay unreliability at the 1 mg dose are the aforementioned study results to be viewed as reliable by OCPB. If the answer is yes you should explain why.

Question #2 - FDA Reply:
The firm's response is acceptable.

Question #3 - FDA Reply:

FDA Reply:
You state" The conclusions drawn from these analyses were that where applicable, i.e., at the dose range of 2-10 mg for studies CC547 and CD596 (all
male subjects), and at the dose range of 0.5-2 mg and 1-4 mg (male and female) patient studies TVP-1012/112 and TVP-1012/231, respectively, the model showed dose-proportionality in AUC for PAI following repeated dosing." This response is troubling since you previously stated that your assay for the 1 mg dose was low and not reliable. Are you now stating that in some studies the assay was reliable. You must clarify this point.

Given the level of concern by Dr. Kapcala related to gender and age effects on Tyramine levels, one must be clear on the exposure levels at the 1 mg dose which has been seriously challenged by your statement related to the 1 mg dose and moreover the impact has serious consequences since you stated the assay was not reliable at the 1 mg dose following multiple dosing.

The firm needs to clarify these issues or all study results may be subject to scientific challenge.

CDR Teresa Wheelous, R. Ph.
Senior Regulatory Management Officer
Office of Drug Evaluation I
vision of Neuropharmacological Drug Products
HFD-120
1451 Rockville Pike
Rockville, MD 20852

Telephone (301) 594-2850
Fax (301) 594-2859

Appears This Way
On Original

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Thursday, March 24, 2005 10:00 AM
To: Dennis. Williams (Dennis.Williams@tevaneuro.com)
Subject: Rasagiline Rat Carcinogenicity Data

Dennis,

The following is an information request regarding the rat carcinogenicity data:

In the SAS transport file, TUMOR.XPT, submitted on 11/04/2004 for the rat carcinogenicity study, 6751-109, there are some inconsistencies in the ORGANEXM variable which need to be explained.

Although it was indicated in the new report that the 22 animals in the male medium dose group (1 mg/kg) that survived until terminal sacrifice were re-evaluated in the supplemental examination, the TUMOR.XPT data suggest that for many tissues they were not. In particular, for many tissues about 22 animals have records with ORGANEXM=3 indicating that the tissue was not examined. You need to check that the data is correct as submitted because certain tumors appear to be statistically significant when the data is analyzed as is, yet you reported that there were no tumors that were statistically significant.

In addition, some animals in the male middle dose group have an entry for a particular tissue that has ORGANEXM=3 (i.e., not examined) but then another entry for the same animal and tissue with a particular tumor and ORGANEXM=1. Thus, the two entries give conflicting information. There are other cases where there are two duplicate records which both indicate that a certain organ was not examined. This calls into question all of the data not just the data for the middle dose group so all the data for the rat study should be verified.

Please address these concerns.

Thank you,

Teresa

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Wednesday, March 23, 2005 3:03 PM
To: 'Dennis.Williams@tevaneuro.com'
Subject: Rasagiline Table 4 Safety Question

Dennis,

The following is a info request from the safety reviewer:
QUESTION FOR TEVA:

In Table 4 summarizing the incidence of cardiovascular SAEs (Response to Approvable Letter: Tyramine, pg. 12), four myocardial infactions (Mis) are reported for rasagiline-treated subjects in the placebo-controlled portions of TEMPO, PRESTO and LARGO, and one MI is reported in a placebo-treated subject. On page 70 of the same submission (Response to Approvable Letter: Tyramine), it is stated that three MIs occurred in the adjunct therapy study LARGO (two receiving rasagiline, one during run-in period prior to rasagiline treatment) and two in the monotherapy study TEMPO (both receiving rasagiline).

Could the subject numbers for the 5 subjects experiencing MIs referred to in the two sections decribed above please be provided?

CDR Teresa Wheelous, R. Ph.
Senior Regulatory Management Officer
Office of Drug Evaluation I
Division of Neuropharmacological Drug Products
HFD-120
1451 Rockville Pike
Rockville, MD 20852
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Fax (301) 594-2859

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Wednesday, February 02, 2005 1:04 PM
To: 'Dennis.Williams@tevaneuro.com'
Subject: Rasagiline NDA CMC Question

Dennis,

The CMC reviewer has the following question:

Is there a misprint(?) in the section: Desc-Comp_0.5 mg.pdf (on page 1)?

How are the 0.5 mg tablets marked? Does one side have "GIL" and the other plain?

Or is one side "GIL" 0.5 and the other plain? Or is it "GIL" with 0.5 directly below the "GIL"/

The offending text (lifted from the PDF document) is shown below. What is the 0.5 -- which appears to be just stuck there, doing?

Thanks,

Bill

3.2.P.1 Description and Composition of the Drug Product

Rasagiline mesylate tablets 0.5 mg (expressed as rasagiline base) are provided

as white to off-white, round, flat, beveled tablets. The tablets are debossed

"GIL" on one side. The other side is plain.

0.5

The composition of the rasagiline mesylate tablets, the function of the

Thanks,

CDR Teresa Wheelous, R. Ph.
Senior Regulatory Management Officer
Office of Drug Evaluation I
Division of Neuropharmacological Drug Products
HFD-120
1451 Rockville Pike
Rockville, MD 20852
Telephone (301) 594-2850
Fax (301) 594-2859

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Wednesday, January 19, 2005 1:36 PM
To: Dennis. Williams (Dennis.Williams@tevaneuro.com)
Subject: Rasagiline NDA Info Request and EA update

Dennis,

The following is a safety information request:

In the response to the FDA action letter request regarding the age- and sex-stratified data for cohort study EP002, could the total number of subjects per cell be added to Table 4 (Distribution of MM cases by Sex and Age Category, pg. 6 of 8, Melanoma, Response to FDA Approvable Letter)? We will need this denominator information in order to complete our comparison with the AAD data.

As for the environmental assessment (EA) update, you are correct that the chemist is requesting this for both the .5 mg and 1 mg tablets.

Thanks,
Teresa

CDR Teresa Wheelous, R. Ph.
Senior Regulatory Management Officer
Office of Drug Evaluation I
Division of Neuropharmacological Drug Products
HFD-120
1451 Rockville Pike
Rockville, MD 20852
Telephone (301) 594-2850
Fax (301) 594-2859

Wheelous, Teresa A

From: Jones, M. Lisa
Sent: Tuesday, January 18, 2005 10:51 AM
To: Wheelous, Teresa A
Subject: Question for Teva: EP002 Comparison Table

Hello Teresa,

Could you please forward the following message to Teva regarding rasagiline (21-641). Thanks.

Lisa

Message for Teva:

In the response to the FDA action letter reqest regarding the age- and sex-stratified data for cohort study EP002, could the total number of subjects per cell be added to Table 4 (Distribution of MM cases by Sex and Age Category, pg. 6 of 8, Melanoma, Response to FDA Approvable Letter)? We will need this demoninator information in order to complete our comparison with the AAD data.

M. Lisa Jones, MD MPH
Medical Officer
Division of Neuropharmacological Drug Products
Food and Drug Administration
Phone: (301) 594-5527
x: (301) 594-2858

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Tuesday, January 11, 2005 10:09 AM
To: Dennis. Williams (Dennis.Williams@tevaneuro.com)
Subject: Worldwide Regulatory Actions Update

Dennis,

Regarding your January 10th phone message to clarify which worldwide rasagiline regulatory status documents to forward, a summary of the general actions (i.e.. approved, pending, etc.) would be appropriate. In addition, as mentioned in the phone message and the prior e-mail, a more detailed summary of the safety concerns communicated to you by the other regulatory agencies is also requested. We appreciate that sending every document from other agencies pertaining to a safety concern would be difficult, but a summary along with the major documents (the equivalent of FDA action letters) would suffice. We understand that this will take more time to prepare than the general statement of current regulatory status, and would ask that you send the summary of current regulatory status first, and then the more detailed summary of any communicated safety concerns as it is available. Please do not hesitate to request further clarifications from us as necessary.

Teresa

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Friday, January 07, 2005 10:11 AM
To: 'Dennis.Williams@tevaneuro.com'
Subject: NDA 21-641 Rasagiline 12/7/05 Info Request

Dennis,

The following is are questions from the safety reviewer for Rasagiline:

MESSAGE FOR TEVA:

The Safety Reviewer has the following questions and clarifications regarding the NDA 21-641 (Rasagiline) document "Amendment to Pending Application: Response to FDA Action Letter:"

Attribution of Discontinuations to a Specific Adverse Event:
1. On ISS pg. 80 (Section 7.3) describing TEVA's methods for increasing attribution of discontinuations due to unspecified adverse events, it is stated that "Reexamination of the AE data for these 10 patients [those discontinuing due to unspecified adverse events] revealed that two patients were omitted from the list."

Please provide more information be provided regarding "omitted from the list?" Specifically, which list is being referred to? Were these two cases included among those discontinuing due to unspecified AEs within the initial NDA or 120-day safety update, or are these "new" cases that were not included in the listing within these reports?

Melanoma Cases:
2. In ISS pg. 80 (Section 7.3), a brief summary is provided of a subject who was initially diagnosed with melanoma in situ, which was re-read as a melanocytic nevus. Please provide additional information on this subject (TVP-1012/135 #109), including dose history and date of diagnosis.

3. Pg. 3 of the response to the FDA's melanoma-related questions states "Two additional melanoma cases were observed after database lock and were not included in the calculations below, as not all CRF data are yet available for calculations of patient exposures." Please provide the subject numbers for these two cases, and any other information that is available at this time.

4. Please provide a complete listing of all subjects within the development program having melanoma as an adverse event through the time of the most recent data lock. Include subjects even if the melanoma was later re-classified to another diagnosis or incomplete information is available due to recent recognition.

CDR Teresa Wheelous, R. Ph.
Senior Regulatory Management Officer
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-641
NDA 20-622

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:

We acknowledge receipt on October 8, 2004 of your October 7, 2004 correspondence notifying the Food and Drug Administration that the corporate address has been changed from:

1090 Horsham Road
North Wales, PA 19544

To

425 Privet Road
P.O. Box 1005
Horsham, PA 19044-8005

For the following new drug applications:

NDA 21-641 (rasagiline mesylate) tablets 0.5 mg and 1 mg
NDA 20-622 Copaxone (glatiramer acetate) for injection 20 mg

We have revised our records to reflect this change.

Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD - 120
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call me at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

CDR Teresa Wheelous
Sr. Regulatory Management Officer
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Teresa Wheelous
1/4/05 11:53:58 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: October 27, 2004

To: Dennis Williams or Michael Nicholas	**From:** Teresa Wheelous
Company:TEVA	Division of Division of Neuropharmacological Drug Products
Fax number: 215-591-8820	**Fax number:** 301-594-2859
Phone number: 215-591-8531	**Phone number:** (301) 594-2850

Subject: Action Letter for NDA 21-641 Rasagiline

Total no. of pages including cover:

Dennis and Michael,
The following are clinical pharmacology comments for NDA 21-641 regarding the end of review briefing package and meeting that we had on September 27, 2004:

1. You should do a formal log dose regression on the Tyramine study P94159 to clearly establish if the PK is indeed nonlinear for AUC between the 1 mg and 2 mg doses.

2. You should present detailed calculations showing the individual data for all Pharmacokinetic calculations in Appendix 2 Tables 1 and 2. These Tables should be annotated for easy identification with their EDR origin or the original tables can be presented in proximity to the newly calculated mean values.

3. You should make pharmacokinetic comparisons only to subjects whom exhibit the same pharmacokinetics. For example males in study CD596 (1-20 mg) exhibit nonlinear pharmacokinetics following singe dosing but linear kinetics after multiple dosing (2-10 mg/day). However in study P94159 at multiple doses of 1mg and 2mg/day, the pharmacokinetics appear to be nonlinear on day 9. Therefore it would not be meaningful to compare the multiple dose data from studies CD596 and P94159. This principle should be followed in all of your comparisons across treatment groups.

Document to be mailed: YES ☑NO

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/s/

Teresa Wheelous
11/1/04 10:51:18 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 27, 2004

TIME: 10 AM – 11 AM

LOCATION: WOC 2, Conference Room E

APPLICATION: NDA 21-641 Rasagiline

TYPE OF MEETING: End of Review

MEETING CHAIR: Dr. Katz

FDA ATTENDEES, TITLES, AND DIVISION
Dr. Russell Katz – Division Director, HFD-120
Dr. John Feeney – Group Leader, HFD-120
Dr. Leonard Kapcala – Medical Reviewer, HFD-120
Dr. Lisa Jones – Safety Reviewer, HFD-120
Dr. Andre Jackson – Clinical Pharmacology & Biopharmaceutics Reviewer, HFD-860
CDR Teresa Wheelous – Sr. Regulatory Management Officer, HFD-120

TEVA Pharmaceutical Industries, LTD ATTENDEES AND TITLES:
Teva Neuroscience
Rivka Kreitman, Ph.D, Vice President, Innovative Research and Development
J. Michael Nicholas, Ph.D., Senior Director of Regulatory Affairs
Dennis Williams, R.Ph, Sr. Manager, Regulatory Affairs

Teva Israel
Michal Herskovitz, ChemEng, Senior Director, Global Regulatory Affairs
Ruth Levy, Ph.D., Executive Director, Global Pipeline Development
Noa Leibovitch, Ph.D., Associate Director, Global Pipeline Development
Yael Keenan, Ph.D., Associate Director, Global Clinical Research

Eisai Medical Research
Rena Williams

External Consultants

Darrell Rigel, M.D., Clinical Professor of Dermatology, NYU Medical Center
Ira Shoulson, M.D.

BACKGROUND AND MEETING OBJECTIVES:
The purpose of the meeting is to discuss several of the concerns listed in the clinical section of the FDA'S approvable letter dated July 2, 2004. The topics to be discussed are the Division's recommendations related to tyramine, melanoma, and the use of concomitant antidepressants.

DISCUSSION POINTS:

1. **Teva believes that the results of the tyramine challenge studies together with the phase III experience (total of 58% (1072/1849.5 patient years) of exposure to rasagiline 0.5mg, 1 mg, and 2 mg were without tyramine restriction: 660 patient years on adjunct therapy and 412 patient years on monotherapy) indicate that rasagiline under usual real-life conditions is selective for MAO-B inhibition and can be used safely without dietary restrictions as monotherapy and as add-on therapy to levodopa at the doses recommended in the prescribing information (see attached summary). The attached summary addresses the Agency's concern that the selectivity of rasagiline 1 mg/day for MAO-B has not been adequately demonstrated in the 4 tyramine challenge studies. The Division's approvable letter and proposed labeling indicate that the labeling would need to be revised with respect to tyramine in the absence of an additional confirmatory trial.** ***Teva would like the Division to clarify the wording for the labeling in the absence of this additional trial.***

    - Dr. Katz noted that, absent a compelling argument, the labeling would include prominent language requiring dietary restriction of tyramine if the sponsor did not conduct the study recommended by DNDP to characterize more comprehensively the risk of tyramine-induced hypertensive reactions that may be associated with rasagiline treatment.

    - Dr. Katz also noted that [redacted]

    - The main goal of the recommend tyramine challenge study is to characterize the risk of tyramine-induced hypertensive reactions more comprehensively, especially at higher rasagiline exposures that might be experienced by some patients for various pharmacokinetic reasons.

    - There was much discussion about the study design, and the possible findings of such a study.

    - The sponsor's position is that the tyramine results from already conducted studies show no clinically significant nor serious cardiovascular findings, and therefore, the labeling should not state that a food restriction (relative to tyramine containing products) is needed.

    - The Division's main concerns and reasons for requesting another tyramine challenge study (under fasting conditions) are that : 1) the tyramine challenge

study conducted under fasting conditions is associated with many problems and limitations as outlined in the Approvable letter; and 2) the bioavailability of tyramine administered with food and shortly before or after meals was not validated and thus the reliability of the findings in these studies is questionable. It is not clear if the patients who did not experience hypertensive reactions in the tyramine challenge studies associated with food represent true negatives or may represent false negatives because of poor or limited tyramine bioavailability. In addition, there is a suggestion that the 2 mg daily dose of rasagiline is not selective for MAO-B inhibition.

- Dr. Kapcala 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.

- The sponsor is welcome to make the argument in the response to the action letter if a decision is made not to conduct the requested tyramine challenge study.

2. **The Division acknowledged in the approvable letter an apparent increase of risk for melanoma in patients with Parkinson's disease compared to that in the general population. However, the observation of this apparent increased risk was made in patients being treated with dopaminergic therapy which did not include rasagiline. The company has briefly summarized the melanoma issue (summary attached) based on the rasagiline clinical development program and information from other sources, including some recent unpublished results (by Dr. —, which strengthens the connection between melanoma and Parkinson's disease. Also a North American epidemiological cohort study that assessed the prevalence of melanoma in PD patients (EP00-2, submitted in the application) showed that the prevalence of melanoma in PD patients is much higher than in a comparable age and sex-matched population.** ***Based on the above, we believe that a statement in the rasagiline labeling that informs health care professionals of the apparent increased risk of melanoma with dopaminergic therapy and/or Parkinson's disease should be included. Does the Division agree?***

    - No, the Division does not agree that this proposal adequately informs the health care professional of the seriousness of the concern, with rasagiline, and a statement should be placed ir — to adequately inform.

    - The sponsor believes that the melanoma occurrence is Parkinson's related and not drug related, and should be stated as a PRECAUTION —

3. **The Agency stated in their proposed labeling that the concomitant use of antidepressants was not recommended. In addition, there is wording that states that although a small number of patients were concomitantly treated with antidepressants, the numbers were not adequate. This wording has a comment from the Division to verify the numbers cited (tricyclics n= –, SSRI n= — in the FDA**

proposed labeling. In the rasagiline clinical program, about 283 (see attached table) rasagiline treated patients received antidepressants (tricyclics n= ~ SSRI n= ~ and ~). *We believe that our experience with rasagiline and concomitant antidepressants indicates they can be used safely with the appropriate prescribing information. Does the Division agree?*

- Because this is a relatively rare phenomenon, the standard language and location was provided in the approvable labeling offered by the Division. The increased numbers presented by the sponsor do not mitigate this potential risk.

- The Division is not aware of information that supports the removal of fluoxetine from other antidepressants, and thus, fluoxetine should be included with the other SSRIs.

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/s/

Russell Katz
12/1/04 04:42:00 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-641

TEVA Pharmaceutical Industries, Ltd.
Attention: J. Michael Nicholas, Ph.D.
1090 Horsham Road
North Wales, PA 19454

Dear Dr. Nicholas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rasagiline Mesylate 1 mg Tablet.

We also refer to your July 29, 2004, correspondence, received July 30, 2004, requesting a meeting to discuss several recommendations provided in the July 2, 2004, end of review Agency letter.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Monday, September 27, 2004
Time: 10 AM – 11 AM
Location: WOC II, 1451 Rockville Pike, Conference Room E, Rockville, MD 20852

CDER participants: Dr. Russell Katz, Dr. John Feeney, Dr. Leonard Kapcala, Dr. Judith Racoosin, Dr. Lisa Jones, CDR Teresa Wheelous

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at wheeloust@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: CDR Wheelous x5504; the division secretary, x 2850.

Provide the background information for this meeting (three copies to the NDA and six (6) desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by August 30, 2004, we may cancel or reschedule the meeting.

If you have any questions, call me, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

CDR Teresa Wheelous
Sr. Regulatory Management Officer
Division of Neuropharmacological Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

Teresa Wheelous
8/9/04 03:59:31 PM

Executive CAC
June 8, 2004

Committee: Abby Jacobs, Ph.D., HFD-540, Acting Chair
Joseph Contrera, Ph.D., HFD-900, Alternate Member
Al DeFelice, Ph.D., HFD-110, Alternate Member
Lois Freed, Ph.D., HFD-120, Team Leader
Paul Roney, Ph.D., HFD-120, Presenting Reviewer

Author of Minutes: Paul Roney, Ph.D.

NDA 21-641
Drug Name: Rasagiline (Agilect)
Sponsor: Teva Pharmaceuticals

Mouse Carcinogenicity Study
CD-1 mice were administered rasagiline orally (by gavage) at doses of 0, 1, 15 or 45 mg/kg for two years. The mice tolerated these doses without notable toxicity. Mortality at the high dose was comparable to control values and final mean body weights were within 10% of control values. A significant positive trend in the incidence of lung neoplasms (adenomas/carcinomas combined) was observed in male mice ($p=0.0007$). The increase in combined adenomas/carcinomas was significant in the high dose males ($p=0.0045$). There was also a near significant trend in the incidence of lung carcinomas alone in male mice ($p=0.0065$, FDA significance criteria is $p\leq0.005$ for trend tests) and a near significant increase in the incidence of combined adenomas/carcinomas in mid-dose males ($p=0.04$, FDA significance criteria is $p\leq0.01$ for pair-wise comparisons). The sponsor suggested that the incidence of lung neoplasms was within historical control range, but an examination of studies conducted within three years of this study showed that the incidence in control males was comparable to the control values in the present study. This would suggest that the increase in lung neoplasms observed in this study is above the historical control range as well. In female mice, a positive trend in the incidence of lung neoplasms (adenomas/carcinomas combined) was observed. The trend was not statistically significant ($p=0.0071$); however, female mice had lower systemic exposure to rasagiline than males (the AUC in high dose females was 5,613 ng-hr/ml compared to 15,673 ng-hr/ml in high dose males) which would lower the probability of detecting tumors in females. It did not appear that an MTD was achieved in females.

Rat Carcinogenicity Study
Rasagiline was administered orally (by gavage) at doses of 0, 0, 0.3, 1 or 3 mg/kg in male Sprague-Dawley rats and at doses of 0, 0, 0.5, 2, 5 or 17 mg/kg in female Sprague-Dawley rats for two years. The high dose in both sexes exceeded the MTD as indicated by greater than 20% decrements in mean body weight compared to controls. No significant increase in tumor incidence was observed at the high dose. Histopathology was not conducted on a full battery of tissues in terminally sacrificed rats in the low and mid dose groups.

Executive CAC Recommendations and Conclusions:

Mouse carcinogenicity study: the Committee agreed that the mouse study was adequate, and concluded that the mouse study was positive for tumors in males (increased incidence of combined lung adenoma/carcinoma). There was an increase in the incidence of lung adenoma/carcinoma in females. Although the increase was not statistically significant, the Committee concluded that the finding in females should not be dismissed considering the increase in the same tumor types in male mice.

Rat carcinogenicity study: the Committee agreed that the rat study was adequate. However, the Committee could not reach a final conclusion regarding the rat study, because the high dose was associated with an excessive effect on body weight (i.e., >10% decrease in mean body weight compared to controls) in both males and females and complete histopathology was not done on the low and mid-dose groups. The Committee recommended that the sponsor conduct histopathology on the low and mid-dose groups and submit the results for evaluation.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

/Division File, HFD 120
/LFreed, HFD-120
/PRoney, HFD-120
/TWheelous, HFD-120
/ASeifried, HFD-024

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/s/

Abby Jacobs
6/14/04 12:55:23 PM

[redacted] JUN 14 [redacted]

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 7, 2004

FROM: Jacqueline A O'Shaughnessy, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 6/8/04
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering NDA 21-641, Rasagiline Mesylate Tablets, Sponsored by Teva Pharmaceutical Industries, Ltd.

TO: Russell G. Katz, M.D.
Director
Division of Neuropharmacological Drug Products
(HFD-120)

At the request of HFD-120, the Division of Scientific Investigations conducted an audit of the following pharmacodynamic interaction study:

> **Protocol P94159:** Pharmacodynamic Interaction Study between TVP-1012 and Oral Tyramine after Repeated Oral Administration of 1, 2 mg/Day TVP-1012 or 10 mg/Day Selegiline for Ten Days in Three Groups of Nine Normal Healthy Volunteers.

This study was conducted by [redacted]. Dr. [redacted] retired several years ago and was not present during the inspection. Instead, [redacted] M.D. (co-investigator) provided relevant information. Following the inspection (5/3-7/04), Form FDA 483 was issued (attached). The objectionable findings and our evaluation are as follows:

1. There are no records of the foods consumed by the study subjects during their study participation, to document that the food restrictions in the protocol were complied with.

The clinical site stated that subjects consumed [redacted] "standard meals" that did not contain foods restricted by the

protocol. However, records (e.g., a menu for the meals) were not maintained to document the composition of these meals, especially for biogenic amines. Furthermore, while the co-investigator claimed that the protocol was followed with regard to fasting requirements, the site only provided the case report form (CRF) to support this claim. The CRF contained a statement to verify that subjects were on an empty stomach since 2100 hours the day before, but the actual time of the previous meal was not recorded. Also, pre-printed information on the CRF concerning the meals (e.g., on day 8, no breakfast, lunch at 6 hours, dinner at 12 hours) does not confirm when meals were actually served. It should be noted that subjects were confined to the clinical unit during dosing periods.

2. **Lab reports from the contract (clinical) laboratory were not signed or initialed and dated by study physicians, documenting their review of same in a timely manner.**

   At the time of this study, the site did not sign and date lab reports to document review. The firm has since changed its procedure.

3. **For numerous blood pressure readings, the actual time of measurement was not recorded. For those instances where the actual time of measurement was recorded, there is no documentaion that the times of measurement were 100% audited to assure compliance with the protocol.**

   Blood pressure (BP) was measured either manually or by a BP machine. The co-investigator stated that, in general, automated measurements were taken during the tyramine challenge on days 8-10. Manual BPs were recorded directly on the CRF that was preprinted with protocol-defined intervals; the actual time of the manual BP readings was not documented. Furthermore, while the BP machine recorded actual times, the site did not confirm that the time of the automated readings conformed to the protocol-required collection times (e.g., every five minutes from 0.5-3 hours post-dose on day 8).

After the inspection had taken place, the review division requested information on the following issues:

- The protocol stated that doses of 3 and 4 mg rasagiline would be tested. However, the final report only discussed doses of 1 and 2 mg rasagiline.

The rasagiline doses of 3 and 4 mg were not administered at — because TEVA decided to stop the study.

- The protocol defined when BP would be measured (e.g., on day 8 at 0, 0.5 hours and every five minutes thereafter up to 3 hours, etc.). However, the final report stated that minute by minute BPs were recorded when a subject was close to the 30 mm Hg endpoint.

The possibility cannot be excluded that these additional BP measurements themselves influenced BP (e.g., "white coat phenomenom"). The co-investigator stated that "during the period of tyramine effect" (typically 10-15 minutes), BPs were collected at one minute intervals, at the request of the sponsor. The site stated that for the report, BPs were reported at five minute intervals.

- Was there any documentation at the clinical site regarding the standardization of the tyramine lots used?

The FDA investigator had no information beyond the lot numbers of tyramine used. However, it should be noted that records of lot standardization are not usually maintained at the clinical site.

Conclusion:

Following the above inspection, the Division of Scientific Investigations concludes that:

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.

After you have reviewed this memo, please append it to the original NDA submission.

Jacqueline A O'Shaughnessy, Ph.D.

Final Classification:

— - VAI

cc:
HFA-224
HFD-45/rf
HFD-48/O'Shaughnessy/Himaya/cf
HFD-120/Wheelous/Kapcala
HFR-SE2560/Rinc
Draft: JAO 6/4/04
Edit: MFS 6/4/04, MKY 6/7/04
DSI: — O:\BE\eircover\21641tev.ras.doc
FACTS # —

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Room 272, 7520 Standish Place Rockville, MD 20855-2737 U.S.A.	May 3-7, 2004 FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: M.D., Chief Executive Officer and Head of Clinical Operations

FIRM NAME	STREET ADDRESS
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
	Bioresearch / Clinical Investigator

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

The following observations relate to study P94159 entitled "Pharmacodynamic Interaction Study between TVP-1012 and Oral Tyramine after Repeated Oral Administration of 1, 2 mg/Day TVP-1012 or 10 mg/Day Selegiline for Ten Days in Three Groups of Nine Normal Healthy Volunteers".

1. There are no records of the foods consumed by the study subjects during their study participation, to document that the food restrictions in the protocol were complied with.

2. Lab reports from the contract (clinical) laboratory were not signed or initialed and dated by study physicians, documenting their review of same in a timely manner.

3. For numerous blood pressure readings, the actual time of measurement was not recorded. For those instances where the actual time of measurement was recorded, there is no documentation that the times of measurement were 100% audited to assure compliance with the protocol.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Roy R. Rinc, Investigator	May 7, 2004

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20855

CLINICAL INSPECTION SUMMARY

DATE: April 7, 2004

TO: Teresa Wheelous, R.Ph., Senior Regulatory Project Manager
Leonard Kapcala, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-641

APPLICANT: Teva Neuroscience

DRUG: Rasagiline Mesylate

THERAPEUTIC CLASSIFICATION: Type S

PROPOSED INDICATION: Parkinson's Disease

CONSULTATION REQUEST DATE: November 21, 2003

ACTION GOAL DATE: July 5, 2004

I. BACKGROUND:

Rasagiline mesylate is an irreversible monoamine oxidase (MAO) inhibitor with high selectivity towards the B form of the enzyme. It is five times more potent than selegiline, the MAO inhibitor, approved for its use in Parkinson's Disease. In this application, the sponsor has requested the use of rasagiline tablets in both early and advanced Parkinson's Disease. The application included the results from the pivotal protocols TVP-1012/133 (PRESTO) entitled "A Multicenter, US and Canada, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study, for the Efficacy, Tolerability and Safety of Rasagiline Mesylate in Levodopa Treated Parkinson's Disease Patients with Motor Fluctuations", and TVP-1012/232 (TEMPO) entitled "A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Phase III Clinical Study, for the Efficacy, Tolerability and Safety of Two Doses of Rasagiline Mesylate in Early Parkinson's

Disease (PD) Patients Not Treated with Levodopa."

Protocol TVP-1012/133 (PRESTO)

The study was a randomized, double-blind, placebo-controlled, parallel group, multicenter study conducted in levodopa treated PD subjects with motor fluctuations for 26 weeks. Following a screening visit and screening period to ensure that subjects met all enrollment criteria and could accurately complete home diaries, subjects were randomly assigned to treatment either rasagiline 0.5 mg, 1.0mg or placebo once daily at the baseline visit. Levodopa dose could be decreased for the first 6 weeks of the study period at the discretion of the investigator but remained constant for the last 20 weeks. Subjects had follow up visits at 3, 6, 10, 14, 20 and 26 weeks after baseline for efficacy and safety monitoring. A 24-hour diary in which subjects rated themselves at home as "on without dyskinesia or without troublesome dyskinesias", "on with troublesome dyskinesias", "off", or "asleep" every half hours was completed for 3 consecutive days immediately prior to randomization (baseline), week 6, 14 and 26 (termination) visits. Additionally, subjects monitored their blood pressure (BP) before and at 45 and 90 minutes after the main meal of the day for seven days prior to baseline, week 3 and 26. The primary efficacy endpoint was the mean total daily "off" time during treatment. The mean total daily "off" time was measured through subjects' 3 daily dairies prior to randomization (baseline) and 9 daily diaries during treatment: 3 diaries prior to week 6, 3 diaries prior to week 14 and 3 diaries prior to week 26 (termination).

Protocol TVP-1012/133A Tyramine Challenge Sub-study

This sub-study was performed on the last day of the 26-week study period. The aim was to evaluate the effect of an oral dose of tyramine (50 mg, immediately after a low tyramine containing meal) in PD subjects treated with rasagiline or placebo for 26 weeks. Hemodynamic parameters (BP, pulse and ECG) were measured at baseline before ingesting tyramine and for at least 4 hours after tyramine ingestion. To prevent unblinding in case of tyramine reaction, the protocol required that the investigator and coordinator roles for this substudy were not carried out by the same individuals who performed their roles in the PRESTO study.

Protocol TVP-1012/232 (TEMPO)

The study was a randomized, double-blind, placebo-controlled, parallel group, multicenter study. The double blind design was maintained during the entire study; a 26-week placebo-controlled treatment was followed by a 26-week active treatment. Subjects were randomized to 1 to 2 mg daily doses of rasagiline or placebo. The study was designed with no dietary tyramine restrictions. The primary efficacy measure was the change in Unified Parkinson's Disease Rating Scale (UPDRS) total scores, calculated from baseline (week 0) to last observed value before additional anti-Parkinson therapy was administered, comparing rasagiline 1 and 2 mg/day with placebo/2mg.

Protocol TVP-1012/232 Tyramine Challenge Sub-study

A tyramine tolerance assessment was based on the comparison of the number of subjects experiencing one of the primary outcome measures (i.e., increase in blood pressure, bradycardia, significant ECG changes) following ingestion of 75 mg tyramine, mixed with food. After the tyramine dose, subjects are monitored with BP, pulse and serial ECG for up to 4 hours following tyramine ingestion.

As per the request of the Review Division (HFD-120), inspection assignments were issued in December 2003 for domestic sites: Drs. Feigin, Hurtig and Colcher/Siderowf. The Review Division has identified that these investigators enrolled a significant number of subjects in the study.

II. RESULTS (by site):

NAME	Protocol (Site #)	Location	ASSIGNED DATE	DATE EIR RECEIVED	CLASSIFICATION
Andrew Feigin, M.D.	232: TEMPO and substudy (site 55)	Manhasset, NY	12/15/2003	02/09/2004	NAI
Howard Hurtig, M.D.	232: TEMPO (site 18)	Philadelphia, PA	12/15/2003	03/04/2004	VAI
Amy Colcher, M.D.	133: PRESTO (site 18)	Philadelphia, PA	12/15/2003	03/04/2003	NAI
Andrew Siderowf, M.D.	133a: substudy (site 18)	Philadelphia, PA	12/15/2003	03/04/2004	NAI
Sponsor: Teva Neuroscience	133, 133a and 232	North Wales, PA	02/05/2004	03/08/2004	NAI

1. Andrew Feigin, M.D. (Protocol TVP1012/232 TEMPO; Site 55)

a. What was inspected: At this site, 16 subjects were enrolled in protocol 232(TEMPO) and six subjects entered into the tyramine substudy. An audit was done on source records from 6 subjects entered into the TEMPO study including 4 of these subjects entered in tyramine substudy. Inspection reviewed the source documents, CRFs and compared with data listing (primary efficacy and adverse events) provided by the sponsor in the NDA submission.

b. Limitations of inspection: N/A.

c. General observations/commentary:

According to the establishment inspection report, there was adequate documentation to ensure that all audited subjects did exist and were available for the duration of their stated participation in the study.

The site conducted study 232 and tyramine substudy according to the protocol. However, it

was noted that the site enrolled two patients who did not meet all eligibility criteria. Subject 267 was 32-year old upon entry into the study as the age specified in the protocol was 35 years or older. Subject 264 did not meet the washout period for Levodopa. In memo to file for each of these 2 subjects, it was noted that the sponsor was notified and waiver was granted.

Adverse events and one SAE were reported to the sponsor, the IRB and in the data listing. No underreporting of adverse events noted. All subjects participated in the study signed the informed consent.

No Form FDA-483 was issued at the end of inspection. No objectionable condition noted. However, the 42-week and 52-week active treatment phase data for subject 267 and the 52-week data for subject 583 recorded in their source records and in the case report forms were not included in the data listing provided by the sponsor for the audit.

d. Recommendation:

DSI suggests the review division to check in the NDA data listing (UPDRS scores) regarding the missing data at time points as stated for above 2 subjects. Overall, data appear acceptable. Data appear acceptable.

2. Howard Hurtig, M.D. (Protocol TVP1012/232 TEMPO; Site 18)

a. What was inspected:

At this site, 26 subjects were screened and 22 subjects were enrolled in protocol 232(TEMPO). Ten subjects entered into the tyramine substudy. An audit was done on source records from 9 subjects entered into the TEMPO study including 8 of these subjects entered in tyramine substudy.

b. Limitations of inspection: N/A

c. General observations/commentary:

Inspection reviewed the source documents, CRFs and compared with data listing (primary efficacy and safety data) provided by the sponsor in the NDA submission. According to the establishment inspection report, there was adequate documentation to ensure that all audited subjects met all inclusion/exclusion criteria and were available for the duration of their stated participation in the study.

The site conducted study 232 and tyramine substudy according to the protocol. There were no discrepancies noted among the data recorded in the source records, in the case report forms and the data listing for primary efficacy variable (UPDRS scores) and safety data listing provided by the sponsor for the audit.

Adverse events and one SAE experienced by subject 097 who had a laproscopic cholecystectomy for cholelithiasis were reported to the sponsor and the IRB. No underreporting of adverse events noted. All subjects participated in the study signed the informed consent.

Regarding the tyramine testing, as suggested by the review division, we reviewed the data with respect to fasting/non-fasting requirements; dietary/drug restrictions; eating before, during or soon after oral tyramine, use or non-use of apple sauce with tyramine, appropriate protocol specifically timed collections of blood pressure and pulse for tyramine testing and timing specification of other procedures performed. From the subjects' records reviewed, no discrepancies noted between the source documents, the CRF and the data listing.

No Form FDA-483 was issued at the end of inspection. However, the following issues were discussed:

- The screening EKG of subject 098 showed the heart rate of 119. Dr. Hurtig reviewed and signed the EKG. However, he did not include the date of his review and his comments on clinical significance of such results, prior to enrollment of this subject. Based on subsequent visits' EKGs, the subject continued to have tachycardia throughout the study.
- There was no date on the TEMPO screening source document for subject 543 to show when the screening was done.
- There was no date on the TEMPO week 4 visit on the source document for subject 99 to show when the week 4 was.

d. Recommendation: Overall, data appear acceptable.

3. Amy Colcher, M.D. (Protocol TVP1012/133: PRESTO; site 18)

a. What was inspected:

Seventeen subjects were screened, 16 entered the study, 5 dropped out, and the remaining 11 were considered evaluable. Study source documents were compared to CRFs and data listing.

b. Limitations of inspection: N/A

c. General observations/commentary:

All subjects signed the informed consent. No Form FDA-483 was issued. No major discrepancy among the source documents, CRF and primary efficacy data listing. No underreporting of AE noted.

d. Recommendation: Overall, data appear acceptable.

4. Andrew Siderowf, M.D. (Protocol TVP1012/133: PRESTO; site 18)

a. What was inspected:

At this site, 17 subjects were screened and 16 subjects were enrolled in protocol 133(PRESTO) under Dr. Colcher as the clinical investigator. To prevent unblinding in case of tyramine reaction, the investigator and coordinator roles for this substudy were not carried out by the same individuals who performed their roles in the PRESTO study. Dr. Siderowf was the clinical investigator for the tyramine substudy. Five subjects (# 109, 110, 112, 114 and 118) entered into the tyramine substudy. An audit was done on source records from all subjects entered in tyramine substudy. Inspection reviewed the source documents and the CRFs and compared with data listing provided by the sponsor in the NDA submission.

b. Limitations of inspection: N/A

c. General observations/commentary:

According to the establishment inspection report, there was adequate documentation to ensure that all audited subjects met all inclusion/exclusion criteria and were available for the duration of their participation stated in the study.

The site conducted study TVP-1012/133a tyramine substudy according to the protocol. Regarding the tyramine testing, as suggested by the review division, we reviewed the data with respect to fasting/non-fasting requirements; dietary/drug restrictions; eating before, during or soon after oral tyramine, use or non-use of apple sauce with tyramine, appropriate protocol specifically timed collections of blood pressure and pulse for tyramine testing and timing specification of other procedures performed. From the subjects' records reviewed, no discrepancies noted between the source documents, the CRF and the data listing.

Subject 118 (0.5 mg rasagiline treatment group) experienced significant elevation of blood pressure (i.e., >30 mmHg increase from the mean baseline systolic BP value) after the tyramine ingestion. The subject was monitored accordingly. This subject who experienced a reaction to the tyramine did not require pharmacological intervention. No discrepancies in BP and heart rates values noted between the source documents, the CRF and the data listing.

No underreporting of adverse events noted. All subjects participated in the study signed the informed consent.

No Form FDA-483 was issued at the end of inspection. The minor discrepancies were discussed: not signing and dating of a memo to file dated 9/4/01 and investigational supplies shipment and receipt verification form.

d. Recommendation: Data appear acceptable.

5. Sponsor Inspection: Teva Neuroscience

The inspection of TEVA was conducted as a routine Sponsor/Monitor/CRO inspection assignment, to review the practice as sponsor and monitor for protocols TEMPO and

PRESTO. The FDA field investigator examined the firm's sponsoring and monitoring operating policies and procedures, and study data from TEMPO and PRESTO was compared to the firm's data listings for accuracy. No data discrepancies or deficiencies from regulations were found.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted based on the limited numbers of the study subjects' records inspected. Overall, data from these centers that had been inspected appear acceptable for use in support of this NDA.

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAI-RR= Deviation(s) form regulations, response received and reviewed. Data acceptable
OAI = Significant deviations for regulations. Data unreliable

cc:
NDA 21-641

HFD-45/Division File / Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U
HFD-46/Khin
HFD-46/George GCPB1 Files

rd:NK:4/7/04-4/8/04

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

/s/

Ni Aye Khin
4/8/04 05:12:17 PM
MEDICAL OFFICER

Khin U
4/8/04 05:17:23 PM
MEDICAL OFFICER

C

31 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

__ § 552(b)(4) Draft Labeling

Wheelaus

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 4, 2003

TO: Associate Director
International Operations Drug Group
Division of Field Investigations (HFC-130)

FROM: C.T. Viswanathan, Ph.D. CTV 12/10/03
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2004 **High Priority CDER User Fee NDA**, Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-641
DRUG: Rasagiline Mesylate Tablets
SPONSOR: Teva Pharmaceutical Industries Ltd.
P.O. Box 8077, Kiryat Nordau,
Netanya, Israel

This memo requests that you arrange for an inspection of the following pharmacodynamic interaction study. **Due to user fee deadline, the inspections must be completed before March 15, 2003.**

Study P94159: Pharmacodynamic Interaction Study between TVP-1012 and Oral Tyramine after Repeated Oral Administration of 1, 2 mg/Day TVP-1012 or 10 mg/Day Selegiline for Ten Days in Three Groups of Nine Normal Healthy Volunteers

Clinical site:

Clinical Investigator:

Sponsor Contact: Ms. S. Oren
Teva Pharmaceutical Industries Ltd.

P.O. Box 8077, Kiryat Nordau,
Netanya, Israel
Tel: (972) 9.639.758
Fax: (972) 9.639.851

This is a phase I, double-blind, placebo-controlled, pharmacodynamic interaction study with subjects randomized to three parallel treatment groups. Thirty subjects were enrolled in the study. Nine subjects in each group completed the study. All subjects in each parallel treatment group underwent 2 subsequent treatment periods. In Period 1, all subjects received single-blind, under fasting conditions, placebo for 10 days with concomitant escalating doses of tyramine for the last 3 days. In Period 2, all subjects received under fasting conditions, double-blind treatment of TVP-1012 (1 mg/day or 2 mg/day), selegiline (10 mg) or placebo for 10 days as folllows: Group 1: 6 subjects received 1 mg TVP-1012 per day and 3 subjects received placebo; Group 2: 6 subjects received 2 mg TVP-1012 per day and 3 subjects received placebo; Group 3: 6 subjects received 10 mg selegiline per day and 3 subjects received placebo. Subjects in all 3 groups received concomitant escalating doses of tyramine for the last 3 days. The 3 groups were studied sequentially starting with group 1. Treatment for the next group started only after a careful assessment of the tolerability and pharmacodynamics of the previous group.

The interaction between TVP-1012 (rasagiline) or selegiline and tyramine was evaluated by measuring the pharmacodynamic end-point[1] in the ITT cohort[2] and the completed cohort[3].

Please verify that the protocol was followed with respect to (1) the fasting requirements, (2) dietary and drug restrictions, (3) food intake before, during or 'soon' after oral tyramiine, (4) use/non-use of applesauce with tyramine, (5) timing for measurement of blood pressure and pulse rate after oral tyramine dose, and (6) timing of blood draw and other procedures like ECG. Please have the records of all study subjects audited, including 100% of the informed consent forms. **Please determine if the patients met the protocol inclusion/exclusion criteria.** The

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[1] The dose of tyramine that induced an increase in systolic blood pressure of 30 mm Hg or more as determined by the difference between the actual systolic blood pressure (sbp) value after tyramine administration and the sbp value immediately before tyramine administration (baseline measurements at days 8, 9, and 10).

[2] The ITT cohort consisted of all subjects randomized in the study.

[3] The completed cohort consisted of all subjects who completed the study according to the protocol.

subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accounting, etc., the files of communication between the clinical sites and the sponsor should be examined for their content.

Following identification of the investigator background material will be forwarded directly.

A member of the Bioequivalence Team from the Division of Scientific Investigations may participate in the inspection.

Headquarters Contact Person: Nilufer M. Tampal, Ph.D.
(301) 594-2457

cc:
HFD-45/RF Acft
HFD-48/Tampal/Himaya /CF
HFD-120/Wheelous
Draft: NMT 12/05/03
Edit: MKY MKY 12/5/03
DSI: O:\BE\assigns\bio21641.doc
FACTS: ✓

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA21-641

TEVA Pharmaceuticals
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 September 5, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rasagiline mesylate 1 mg Tablet

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on November 4, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
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/

Russell Katz
10/30/03 11:38:35 AM

PRE-NDA MEETING MINUTES

DATE: **April 30, 2003**

TIME: **10 AM**

LOCATION: **WOC II conference Room E**

APPLICATION: **IND 45,958 Rasagiline Mesylate for Parkinson's**

TYPE: **Pre-NDA**

ATTENDEES

FDA

NAME	TITLE & DIVISION
Dr. Russell Katz	Division Director HFD-120
Dr. John Feeney	Group Leader HFD - 120
Dr. Kevin Prohaska	Medical Reviewer HFD-120
Dr. Barry Rosloff	Pharmacology Team Leader HFD-120
Dr. Judith Racoosin	Safety Team Leader HFD-120
Dr. Martha Heimann	CMC Team Leader (Acting)
Dr. Andre Jackson	Clinical Pharmacology & Biopharmaceutics Reviewer HFD-860
Dr. Raman Baweja	Clinical Pharmacology & Biopharmaceutics Team Leader HFD-860
Ms. Teresa Wheelous	Senior Regulatory Management Officer

TEVA Neuroscience, (USA)

Rivka Kreitman, Ph.D.	Innovative Research & Development
J. Michael Nicholas, Ph.D.	Sr. Director, Regulatory Affairs
Michael Capone	Sr. Manager, Regulatory Affairs
Dennis Williams	Regulatory Affairs
Phyllis Salzman, Ph.D.	Medical Research Director

TEVA Israel

Michal Hershkovitz	Global Regulatory Affairs Director
Ruth Levy, Ph.D.	Corporate Sr. Director, Global Pipeline Development
Naim Sayag, Ph.D.	Assoc. Director, Project Manager
Sheila Oren, M.D.	Assoc. Director, CNS Clinical Program
Esther Lobel, Ph.D.	Assoc. Director, Global Regulatory Affairs
Noa Leibovitch, Ph.D.	Project Leader, Global Pipeline Development
Hanna Gavish, Ph. D.	Manager, Medical Writing Unit
Eli Eyal	Team Leader, Statistical & Data Management

BACKGROUND:

The February 25, 2003 Pre-NDA meeting request was granted on March 11, 2003. The briefing document dated April 1, 2003 was received on April 2, 2003.

DISCUSSION QUESTIONS:

CMC

Teva intends to claim a categorical exclusion from submitting an environmental assessment. In appendix C, we have provided our reasoning for the categorical exclusion. Is this acceptable?

- Yes, this is acceptable

CLINICAL

- The proposed timing for the application is August/September 2003.
- Several studies relative to the concern for melanoma issue are still ongoing and will not be completed by the expected date of submission. The sponsor was informed that significant data submitted late in the review cycle may result in an extension of the review clock or not be reviewed during the first cycle.
- Studies relative to tyramine interaction have been completed and will be submitted during the initial submission.

1. *Is the presentation of the key efficacy tables of the pivotal clinical trial reports, as presented in Appendices F, G, H acceptable?*

   - Yes, and for patients moving into the active phase in TEMPO it would be helpful to perform a sensitivity analysis of the results obtained

2. *Teva would like to receive the Agency's input on the presentation of exposure data, located in Section 11.2. Are the proposed exposure data acceptable for the submission of the NDA?*

   - The chronic exposure data appears to be adequate at 6 and 12 months. Regarding table 11.2, page 8 of the submission, exposure also needs to be shown by dose.

3. *The benefits and risk section is at present a part of the clinical overview; it appears in the conclusions. Is a stand alone benefit and risk document also required and where should it be located?*

   - A discussion of risk and benefits is required. Its location is up to the sponsor as long it can be easily found.

INTEGRATED SUMMARY OF SAFETY

1. *Teva would like to receive the Agency's input on the presentation of the ISS as described in Appendix I. Specifically, the ISS will summarize safety data from all monitored, protocol-driven studies and will subdivide the Parkinson's population into cohorts. (See Section 11.4.1, p.14 of the briefing package and see appendix I, section 1.6 for definitions of these cohorts. Three of these cohorts include a subset of patients who have been treated for one year or longer. A patient's safety data may appear in more than one cohort. Nevertheless, cohorts will be re-integrated for purposes of summarizing safety (see Section 11.4.2, p. 15,) is this acceptable?*

   - The diagram on page 14 of the submission (11.4.1) does not appear to be consistent with the written descriptions summarized in Appendix 1, section 1.6. The definitions will need to be clarified. We would like all placebo-controlled experience separated from any active control experience. In the active control phase of TEMPO we suggest the sponsor compare all subjects newly randomized to rasagiline to all subjects who continued on rasagiline from the placebo control portion of the study. It might be helpful to define your cohorts as such: placebo-rasagiline vs. rasagiline-rasagiline or something similar. The sponsor clarified that the analysis groups we want (separating the placebo controlled portion of the trial and comparing the placebo-rasagiline and rasagiline-rasagiline groups during the "active treatment" phase) will be included in the study report for TEMPO.

   - The sponsor clarified that the submission only contains a skeletal example of the table listings that will be included in the safety report. For example table 24 (section 5.3.1.1), PC studies: Levodopa Fluctuating patients" will also be completed for all other cohorts in the placebo control studies.

   - The sponsor was reminded we require a complete listing of all deaths, serious AEs, and discontinuations due to AEs.

   - In general we are not concerned with the investigator's assessment of relatedness for any given adverse event. Our primary concern is clear and complete case report forms with relevant lab and imaging results.

   - The sponsor should include a table of common adverse events using an appropriate threshold such as 1%, 2% and greater than the incidence of placebo. Tables that list AEs in descending order of incidence should also be provided organized by body system and preferred term.

   - With regard to calculating the incidences of AEs, SAEs, and discontinuations due to AEs, we made the suggestion to the sponsor that person-time be used in the denominator to calculate rates when there is substantial differences in the time to discontinuation between treatment groups

   - Include "time to event plots" for the most common and serious adverse events such as syncope.

- We suggest performing a person-time analysis when comparing withdrawals as well as deaths

- We recommend the sponsor calculate themortality rates occurring in placebo control trials separately from those occurring in extension trials.

- We request the sponsor submit a list of PCS values for all labs, ECGs etc. We note that 30-mm Hg decrease in SBP may be too high and suggest 20 mm Hg which is consisted with the American Academy of Neurology recommendations. We realize a lower threshold will result in increased noise however a comparison of cohorts should help obviate this concern. We agreed that the sponsor will provide analyses using both the 30mmHg and 20mmHg thresholds.

- The sponsor proposes to use Bazett's correction when performing a QT analysis. They state that rasagiline does not alter heart rate. The sponsor was reminded that Bazett's could over correct and under correct if the drug product causes tachycardia or bradycardia. The sponsor stated that in contrast to what the briefing package says, they are planning to use the Fridericia's correction.

2. *Teva would like to receive the Agency's input on the presentation of special safety evaluations (see appendix I, section 10). Specifically, Teva plans to submit stand-alone overviews of potential for tyramine interaction and incidence of melanoma as appendices to the ISS, with summaries of these overviews included in the text of the ISS. Is this acceptable?*

   - Relative to special safety evaluations (tyramine interaction, melanoma in PD), the sponsor's plan to submit stand alone overviews as appendices to the ISS, with summaries of these overviews included in the text of the ISS, is acceptable.

ELECTRONIC FILES

1. *In the electronic filing, TEVA proposed to divide the CTD summaries that would appear in Module 2 into several folders. The Clinical Overview, Non-clinical Overview, and Quality summary will appear in the Summary folder. The Non-clinical written and tabulated summaries will appear in the Pharm/Tox folder with the individual pharmacology / toxicology study reports. The clinical summary will appear in the ClinStat folder with the individual clinical study reports. Is this approach acceptable?*

   - Yes, this is acceptable as long as adequate bookmarks are provided.

2. *The FDA guidance currently requires that for submissions to CDER, the sponsor is required to submit a paper review copy of the technical sections (CMC, Nonclinical, human PK and Bioavailability, and Clinical / Statistical) in addition to the electronic archive copy. Teva proposed to submit this paper review copy only upon the request of the individual technical reviewers. Is this approach acceptable?*

   - We prefer electronic submission to paper. Each reviewer will inform you which section they may want in paper. The medical reviewer requested a hard copy of

the ISS, ISE and section 2.5. Biopharm requested section 5.0.

- The format proposed by the sponsor appears acceptable. We suggest multiple links between documents and other navigating tools to help in the review. All documents should be in adobe acrobat format and searchable. CRT should be provided in SAS transport files. Variables should be well defined in the define.pdf. Embedding links when referencing other study reports for SAEs and deaths will aid in review otherwise a summary should be included in the ISS.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS

- The firm should clearly document any interconversion of the active R-isomer to the less active S-isomer.

- The firm should conduct in vitro isozyme elucidation studies to determine the effect of Rasagiline on other substrates and should also define any isozymes responsible for Rasagiline metabolism.

- The firm should use dissolution data from relevant stability batches, clinical batches and to-be-marketed bio-batches to establish the best dissolution medium and conditions. At least 3 pH ranging media should be investigated. This data should be submitted to FDA with the firm's recommendation as to their proposed medium and conditions based upon the data.

- The firm should retain samples for the batches used in the bio-study.

- The firm should provide data related to the activity of the parent vs. the major human metabolite.

- The preferred population PK format will be transmitted to the sponsor through the project manager.

PRECLINICAL

- We request that the preclinical section of the NDA contain information about any impurities/degradation products which are above the threshold for qualification; in particular we want to know the amounts of these substances present in lots used in each of the pivotal preclinical toxicity studies.

- We request that the preclinical section of the NDA contain a discussion of comparative animal/human metabolism; in particular a discussion of how well the major human metabolites were covered in the pivotal preclinical toxicity studies.

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/s/

Russell Katz
7/15/03 09:08:35 AM

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May 3, 2001

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DUPLICATE

IND 45,958
Rasagiline Mesylate (TVP- 1012)
Serial No. 150
Other: Teleconference Meeting Minutes from April 6, 2001

Dear Dr. Katz
Reference is made to the Investigational New Drug application cited above, originally submitted on August 5, 1994. Reference is also made to a teleconference on April 6, 2001 between the Division of Neuropharmacological Drug Products and Teva Pharmaceuticals. The teleconference requested by Teva was regarding malignant melanoma cases reported in rasagiline clinical trials.

The purpose of the teleconference was to assure the Division that Teva fully recognized the reported cases of melanoma and to date has been diligent to revise the Informed Consent and Investigator's Brochure. Teva would also like the Division to know that the company is taking proactive steps to analyze, monitor, and manage any potential risk.

Teva requested the Division's support to work together in further developing a comprehensive assessment strategy that would serve the interests of all involved in the project development.

Meeting Minutes

Meeting Date: **April 6, 2001**
IND: **45,958**
Drug: **Rasagiline**
Sponsor: **TEVA Pharmaceuticals**
Type of Meeting: **Safety Discussion (Malignant Melanoma Cases)**

Participants: see attached.

Meeting Objective:

Discussion Points (bullets):

- The attached sponsor meeting minutes appear accurate and will serve as official minutes.

Signature, minutes preparer

Teresa Wheelous, R.Ph.
Regulatory Project Manager, DNDP

Concurrence Chair (or designated signatory)

Russell Katz M.D.
Division Director, DNDP

Attachment – sponsor minutes

TVP-1012 Rasagiline Mesylate

FDA Teleconference April 6, 2001 2:00 PM

Teva Pharmaceuticals Participants:

Teva US

Dr. Scott Grossman, Director, Regulatory Affairs
Ms. Linda Knapp, Associate Director, Regulatory Affairs

Teva Israel

Ms. Michal Herskovitz, Director, Regulatory Affairs
Dr. Yafit Stark, Senior Director, Clinical Research
Dr. Hedva Voliovitch, Director, Global Drug Safety and Pharmacovigilance

FDA Division of Neuropharmacological Drug Products Participants:

Dr. Russell Katz, Director
Dr. John Feeney, Supervisory Medical Reviewer
Dr. Judy Racoosin, Safety Team
Mr. Merril Mille, Project Manager

Reference is made to a teleconference held on April 6, 2001 between the FDA Division of Neuropharmacological Drug Products and Teva Pharmaceuticals. The teleconference was requested by Teva regarding a safety issue of five reported malignant melanoma cases.

Dr. Grossman outlined the following history and information for the Division:

On December 8, 2000 an IND safety report (Serial Number 133) was issued describing a case of metastatic melanoma that developed from a pre-existing mole in a 49 year-old female participating in one of the rasagiline clinical trials.

In the IND safety report mentioned above, it was noted that three other patients were diagnosed with malignant melanoma at some point during rasagiline clinical studies TVP-1012/232-233. Each of these three patients had various risk factors that could contribute to the development of the malignancy and one of them had a medical history of melanoma.

Further to the IND safety report, Teva has made every effort to rapidly obtain the pathological reports of these four patients and, in addition, generated an assessment report on "Melanoma in Rasagiline Clinical Program".
This report was aimed at giving further details on the patients and reviewing different aspects of nalignant melanoma and the relation to Parkinson's disease from various literature sources. In parallel, an expert opinion by Dr. DuPont Guerry, Director of Melanoma Program in the University of Pennsylvania Cancer Center, was obtained and attached to the assessment report stating that he does not find compelling evidence to believe that the development of these melanomas is related to

rasagiline treatment.

This assessment report as well as a request for modification of the Informed Consent and a cover letter were sent to the investigators participating in the rasagiline clinical trials in North America on February 8, 2001. The rasagiline Investigator's Brochure was also updated (submitted on February 20, 2001, Serial No. 139).

On March 22, 2001 a fifth case of malignant melanoma was reported to Teva.

The main purpose of this teleconference was to assure the Division that Teva fully recognizes the reported eases of melanoma and has been diligent to revise the Informed Consent and Investigator's Brochure. Teva would also like the Division to know that the company is taking proactive steps to analyze, monitor, and manage any potential risk.

Teva proposes using an epidemiologically based assessment style for evaluating any possible future cases of melanoma. At present, Teva has identified an epidemiological expert, Dr. ., to whom the present relevant documents have been sent for review and assessment. Teva will also be consulting other expert epidemiologists.

We would like to enlist the Division's support to work together in further developing a comprehensive assessment strategy that would serve the interests of all involved in the project development.

Discussion:

Division Questions/Teva Answers:
Note: the information conveyed in these minutes reflects the correct answers. Information relayed in the teleconference may have been slightly different than what is presented here.

1. Q: Were the revised Informed Consents signed by all of the patients enrolled?

   A: The revised Informed Consent was sent to all Ethical Committees of the participating centers. To date, not all IRBs have approved the revised Informed Consent.

2. Q: Were any of the melanoma cases in controlled trials?

   A: There was one patient in trial TVP-1012/232 and one patient in the TVP-1012/232 active extension. The other three patients were in the open-label TVP-1012/233 trial.

3. Q: How long were the patients on treatment? How old were they and where were the melanomas located?

   A: First patient was 13 months in the study (active extension); 74 year old male; temple and hand lesions.

   Second patient was 2.5 months in the study (double-blind, placebo-controlled); 73 year old male; "spot" on forehead.

   Third patient was 19 months on treatment; 56 year old female; arm.

   Fourth patient was 31 months on treatment; 49 year old female; pre-existing mole on the back.

   Fifth patient was 35 months on treatment; 69 year old male; no prior history; shoulder.

   Teva will submit data on exposure, randomized versus open-label.

   Melanoma is a contraindication to Levodopa, but none of the patients were treated with Levodopa when diagnosed with melanoma.

4. Q: It would be useful to know the exposure of patients treated with levodopa versus no levodopa. It would also be useful to see the exposure time, i.e., <2 years/2 years/>2 years, a break down by age, i.e., 40-49, 50-59, etc., and number of patients exposed long term versus short term. Can Teva provide a comprehensive package?

   A: The exposure is estimated at 800 patient years at present, but this needs updating. Teva is

   currently investigating the correlation between melanoma in PD, Levodopa and melanoma, and the prevalence of melanoma in the Teva's patient population in terms of age, PD, geographical location, etc. A comprehensive package will be submitted in one month. Teva will submit the information presently available to the Division immediately.

5. Q: Can background rate information be obtained regarding melanomas and Parkinson's Disease?

   A: Teva will be asking Dr. Burkhart. Does the Division have any other ideas?

Division comment: Teva might try the Mayo Clinic, Rochester Epidemiology Project. They have a good database that deals with Parkinson's Disease.

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/s/

Russell Katz
6/5/01 08:57:33 AM

Meeting Minutes

Meeting Date:	**August 17, 2000 and August 23, 2000**
IND:	**45,958**
Drug:	**TVP-1012 (Rasagiline Mesylate)**
Sponsor:	**TEVA Pharmaceuticals**
Type of Meeting:	**With Sponsor**

Participants: see attached.

Meeting Objective: The need for tyramine restricted diets in study population of TVP-1012/133 (PRESTO) study.

Discussion Points (bullets):

- The attached sponsor meeting minutes appear accurate and will serve as official minutes.

Signature, minutes preparer

Teresa Wheelous, R.Ph.
Regulatory Project Manager, DNDP

Concurrence Chair (or designated signatory)

John Feeney M.D.
Group Team Leader, DNDP

Attachment – sponsor minutes

TVP- 1012 (Rasagiline Mesylate)

FDA Meeting August 17, 2000 2:00 PM

Teva Pharmaceuticals Attendees:

Teva US

Dr. Scott Grossman, Director, Regulatory Affairs
Ms. Linda Knapp, Manager, Regulatory Affairs
Df. Wayne Mulcahy, Senior Director, Clinical Research and Innovative R& D Dr. Phyllis Salzman, Director, CNS Clinical Studies

Teva Israel

Dr. Ruth Levy, Senior Director, CNS Section
Dr. Noa Leibovitch, Project Manager, CNS Section
Dr. Esther Lobel, Senior Manager, Regulatory Affairs, R & D Division
Dr. Sheila Oren, Senior Manager, Clinical Trials
Dr. Hedva Voliovitch, Director, Global Drug Safety and Pharmacovigilance

Consultant

Parkinson's Study Group

Dr. Ira Shoulson, Principal Investigator of PRESTO, Rochester University

FDA Division of Neuropharmacological Drug Products Attendees:

Dr. Russell Katz, Director
Dr. John Feeney, Supervisor, Medical Reviewers
Dr. Kevin Prohaska, Medical Reviewer
Ms. Teresa Wheelous, Project Manager

Reference is made to a meeting held on August 17, 2000 between the FDA Division of Neuropharmacological Drug Products and Teva Pharmaceuticals regarding the future development of TVP-1012 (rasagiline mesylate) for the treatment of Parkinson's disease (PD). The following are Teva Pharmaceuticals' meeting minutes.

After a brief introduction by Dr. Scott Grossman thanking the Division for their time, Dr. Grossman outlined Teva's objective for the meeting. The objective was to have the Division's agreement that protocol TVP-1012/133 (PRESTO), "A Multicenter, US and

Canada, Double Blind, Randomized, Placebo-Controlled, Parallel Group Study, for the Efficacy, Tolerability and Safety of Rasagiline Mesylate in Levodopa Treated Parkinson's Disease Patients with Motor Fluctuations", could proceed without a tyramine diet restriction at the planned rasagiline doses (0.5 and 1.0 mg/day).

A brief Teva presentation was made by Dr. Noa Leibovitch (please see the attached hard copy overheads).

Introductory FDA Comments:

- The Division agrees that it is not necessary to restrict diet in the TVP-1012/133 (PRESTO) study.

- There are no affirmative, formal data to indicate that 1 mg/day of rasagiline ±levodopa may be associated with a tyramine interaction. "Signals" from the 2 mg/day dose of rasagiline in TVP-1012/232 and TVP-1012/132 studies suggested that there might have been an effect of tyramine on blood pressure in patients taking 2 mg/day of rasagiline, there were no "signals" to indicate that there is any risk in 1 mg/day of rasagiline.

- 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.

Discussion:

Division Questions/Teva Answers:

1. Q: Home blood pressure (BP) monitoring is proposed at three weeks. Why not perform the testing earlier?

   A: It seems that some time is needed to develop the sensitivity to tyramine, as a few weeks of dosing may be required to achieve maximal MAO inhibition. The home BP monitoring will actually begin seven days before week 3, approximately two weeks
   after starting the test drug. Patients need about two weeks to settle into the routine of the study and be comfortable with the BP monitoring procedure.

2. Q: What is the rationale for doing the postprandial BP monitoring at 60 minutes? Blood pressure monitoring at 45 and 90 minutes following the main meal may be better that at 60 minutes alone.

   A: The rationale for measuring home BP at 60 minutes following the main meal is based on the TVP-1012/232 (TEMPO) tyramine challenge sub-study. Typically, a tyramine reaction when tyramine is taken with food will take place between 45 to 120 minutes after start of the meal.

3. Q: What is the rationale of doing the tyramine challenge (TVP-1012/133a) at the end of rather than prior to the main trial? Hundreds of patients are being exposed to rasagiline during the main trial. Why not find out early on if there is a tyramine interaction problem?

   A: The patients have a degree of comfort going into the challenge after having participated in the main study, therefore the recruitment into TVP-1012/133a will be more successful and it is important to have as many patients as possible doing the tyramine challenge. It is believed that any observed blood pressure elevations or symptoms possibly associated with increased BP axe potentially unblinding. Furthermore, any possible tyramine reaction may be better seen after a longer treatment period.

4. Q: What is the rationale for the tyramine challenge after meals?

   A: Tyramine bioavailability is lower following a high fat or high protein meal. A fasting challenge with 50 mg tyramine is approximately the same as 200 mg tyramine with food, which is unrealistic. A high tyramine meal may contain approximately 35 mg tyramine, therefore 50 mg of tyramine after a meal reflects a potential "real life situation" regarding tyramine absorption from food.

Conclusions:

- It was agreed that the postprandial home monitoring BP measurements would be done before and at 45 and 90 minutes after the main meal.

- It was agreed that home BP monitoring can be performed between 2 and 3 weeks after the start of the study, as well as at the end of the study before Week 26.

- It was agreed that to represent a more real-world situation the tyramine challenge would be conducted following a meal.

- It was agreed at the subsequent teleconference that the tyramine sub-study challenge (TVP-1012/133a) will be done as proposed at the end of the main study.

- Dietary restriction of tyramine is not required in TVP-1012/122 (PRESTO).

The Division stated that they would like to meet internally to discuss the tyramine challenge study. The Division will follow-up with Teva in the near future.

TVP-1012 RASAGILINE MESYLATE

FDA TELELCONFERENCE
August 23, 2000 1:30 PM

Teva Pharmaceutical Participants:

Teva US

Ms. Majorie Johnston, Senior CRA
Ms. Linda Knapp, Manager, Regulatory Affairs
Dr. Wayne Mulcahy, Senior Director, Clinical Research and Innovative R & D
Dr. Phyllis Salzman, Director, CNS Clinical Studies

Teva Israel

Ms. Michal Hershkovitch, Director, Regulatory Affairs
Dr. Noa Leibovitch, Project Manager, CNS Section
Dr. Ruth Levy, Senior Director, CNS Section
Dr. Esther Lobel, Senior Manager, Regulatory Affairs
Dr. Sheila Oren, Senior Manager, Clinical Trials
Dr. Hedva Voliovitch, Director, Global Drug Safety and Pharmacovigilance

FDA Division of Neuropharmacological Drug Products

Dr. John Feeney, Supervisor, Medical Reviewers
Dr. Kevin Prohaska, Medical Reviewer
Mr.Merril Mille, Project Manager

The Division telephoned today, August 23, 2000, to request a teleconference with Teva Pharmaceuticals regarding protocol TVP-1012/133 (PRESTO). This was a follow-up to the "face-to-face" meeting held on August 17, 2000. At the end of that meeting the Division stated that they would like to internally review Teva's proposed timing and methodology of protocol TVP-012/133a the tyramine challenge sub-study of PRESTO.

Summary of the teleconference:

l, The Division agreed that the tyramine sub-study (TVP-1012/133a) could be done at the end of the double-blind phase of the main PRESTO study (TVP-1012/133), as planned. However, the Division asked that the home blood pressure (BP) monitoring results obtained at Week 3 of PRESTO be reviewed on an ongoing, blinded basis.

2. Teva agreed to the Division's request for ongoing, blinded evaluation of Week 3 home BP monitoring data by the Safety Monitoring Committee (SMC). As each cohort of 60 sequentially enrolled patients completes the Week 3 home BP monitoring procedure, these BP results will be summarized by blinded treatment groups (i.e. Group A, B, and C) and reviewed by the SMC. Data reviews will be cumulative, with each new group of 60 patients' data added to the body of data previously reviewed. Thus, at sequential BP data reviews by SMC, the number of patients with data under examination will increase from 60 to 120, 180, 240, 300, and finally 360.

3. The Division agreed that the plan for data review and identification of signals in home BP measurements by the SMC can be detailed in the working practices of the SMC and does not need to be specified in the protocol.

APPEARS THIS WAY
ON ORIGINAL

END-OF-PHASE II MEETING MINUTES

Meeting Date: June 18, 1997
IND# & Drug Name: 45,958 Rasagiline Mesylate for Parkinson's Disease
Sponsor: TEVA Pharmaceuticals USA
Meeting Chair: Dr. Paul Leber Meeting Recorder: Ms. Teresa Wheelous

FDA Attendees & Titles:
Dr. Robert Temple - Office Director
Dr. Paul Leber - Division Director
Dr. Russell Katz - Group Leader
Dr. James Sherry - Medical Officer
Dr. Todd Sahlroot - Biometrics Team Leader
Ms. Teresa Wheelous - Project Manager
Dr. Vijay Tamara - Biopharmaceutics Reviewer

External Participant Attendees & Titles:
Dr. Karl Kieburtz - Neurologist, Univ. Of Rochester
Mr. Charles LaPree - Assoc. Director.Reg.Affairs
Dr. Ben Zion Weider - V.P. R&D, TEVA
Dr. Wayne Mulcahy - Director Clinical Research
Dr. Sheila Oreli - Clinical Project Manager
Dr.. Ruth Ley - Sr. Director, R&D, TEVA
Ms. Theresa Greaves - Regulatory affairs, TEVA

Meeting Objectives: Preparation of Phase III studies for eventual NDA submission.

CLINICAL:

MAOB Inhibition and Tyramine

*Rasagiline is an irreversible MAO B Inhibitor without amphetamine-like metabolites. The major metabolite, 1-(R)-aminoindan (AI), is pharmacologically active and is not a MAO inhibitor.

*Choice of dose depends upon the relative selectivity of MAOB inhibition.

*With MAOB inhibition there is a concern about possible hypertensive reactions occurring with tyramine and the need to restrict the intake of dietary tyramine.

*Some tyramine/rasagiline combination studies have been performed with administration of up to 800 mg of tyramine.

*There was a discussion about whether or not restrictions on the dietary intake of tyramine should be imposed. It was generally agreed that restrictions should not be imposed, but that the sponsor should propose a plan to challenge

patients with a tyramine rich meal at some point during exposure to rasagiline.

NDA Minimal Study Requirements

*Minimal NDA requirements are: 2 well controlled studies; if the sponsor wishes to obtain a claim for early and late Parkinson's Disease, one study in early Parkinson's and one study in advance Parkinson's (with levodopa) would suffice.

*The specific endpoint (primary outcome = total UPDRS) is defined in advance as the summation of Part I, Part II and Part III only, of the 6 part UPDRS scale.

*From a safety standpoint, the larger the total number of subjects the better, minimum of 300 to 600 subjects on drug for 6 months and 100 for one year.

*The current plan for the primary analysis is to compare the UPDRS at baseline to that at the end of treatment. However, this method does not give experience during the entire course of treatment. A multi-time point course would be helpful in assessing improvement of disease condition, and provides descriptive material that can be placed in labeling.

*The dropout cohort's treatment assessment provides additional information.

ACTION ITEMS:

1. The sponsor will consider the suggestions about adding a tyramine rich meal, and submit phase 3 protocols possibly including a tyramine rich meal.

2. There will be a separate telecon for biopharmaceutics and for biometrics.

3. Project Manager will create and circulate EOP2 meeting minutes.

Signature, minutes preparer:
Concurrence Chair:

cc:
IND 45,958
Div. Files
HFD-120/PLeber
HFD-120/RKatz
HFD-120/JFeeney
HFD-710/TSahlroot
HFD-860/VTammara
HFD-120/TWheelous

draft: 6/24/97
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