CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-641/S-008

SUMMARY REVIEW

Review and Evaluation of Clinical Data

NDA	**21641**
Sponsor:	**TEVA Pharmaceuticals**
Drug:	**rasagiline**
Proposed Indication:	**Treatment of Parkinson's Disease**
Material Submitted:	**Final Study Reports to satisfy Phase 4 Post-marketing Commitment (PMC) to investigate orthostatic blood pressure and pulse timed to rasagiline dosing**
Correspondence Date:	**6/07/07, 2/6/09**
Date Received / Agency:	**6/07/07, 2/9/09**
Date Review Completed	**8/21/09**
Reviewer:	**Leonard Peter Kapcala, MD**

This medical officer review evaluates whether a Phase 4 Post-marketing Commitment (PMC) to investigate orthostatic blood pressure and pulse timed to rasagiline dosing has been met/satisfied. This review provides comments and recommendations for the DNP Director and Team Leader so that recommendations can be made to the sponsor.

1. Introduction / Background

On 5/16/06 the Agency approved rasagiline for the treatment of signs and symptoms of Parkinson's Disease. At the time of approval, the sponsor agreed to several Post-Marketing Commitments (PMCs) including the following PMCs shown in italics :

1. A formal tyramine challenge study in the fasted state. This trial will incorporate the following elements:

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

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

Protocol submission Date: July 30, 2006

Study Start Date: December 30, 2006

Final Report Submission Date: December 30, 2008

2. To investigate orthostatic blood pressure and pulse timed to rasagiline dosing. This will be evaluated in both the tyramine challenge study listed above and the dose proportionality study listed below (no. 4).

The dates of commitments will correspond to the respective dates of the tyramine challenge study and dose proportionality study, respectively.

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

Protocol submission Date: January 20, 2006

Study Start Date: March 30, 2006

Final Report Submission Date: February 28, 2007

The sponsor submitted the final study report for the study investigating dose-proportionality and orthostatic blood pressure and pulse timed to rasagiline dosing (PMC # 4) to fulfill PMC#4 on June 7, 2007. The sponsor also submitted the final study report for the tyramine challenge study investigating also effects of rasagiline timed to dosing on orthostatic blood pressure on 2/9/09.

In the dose proportionality study, the sponsor collected orthostatic (supine and standing) blood pressure and pulse measurements prior to treatment on day -1 and at pre-dose on day 7 (after 7 days of rasagiline treatment; at pharmacokinetic steady state) and at + 30, 60, 90 minutes after dosing in males and females and elderly subjects > 65 years old and "young" subjects (40-60 years old). Subjects received 1, 2, or 6 mg daily under open-label conditions.

In the tyramine challenge study, the sponsor collected orthostatic (supine and standing) blood pressure and pulse measurements prior to treatment and at pre-dose after 13 days of treatment (at pharmacokinetic steady state) and at + 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, , 12, 16, and 24 hours after dosing. Subjects were randomized to receive placebo, 1, 2, 4, or 6 mg rasagiline daily under double-blinded conditions. Another group of subjects were also

studied after 29 days of prolonged treatment with 2 mg rasagiline or placebo for effects on orthostatic VS.

2. Comments

- Orthostatic (supine and standing) VS were collected in the dose-proportionality study and in the tyramine challenge study. Collection of these data satisfy the PMC # 2 to investigate orthostatic blood pressure and pulse timed to rasagiline dosing. in both the tyramine challenge study and in the dose proportionality study.

- The sponsor conducted detailed analyses of orthostatic VS in the different dose groups. These analyses are under under review for the NDA supplement containing the tyramine challenge study. My review of these data analyses will be presented and assessed in my review of that supplement.

- Presentation of the data in the dose-proportionality study are not optimal for assessing the effects of different doses of rasagiline, gender, and age on orthostatic VS at the specified times collected shortly after rasagiline dosing. I will request that the sponsor conduct additional analyses to determine the effects of gender and age on these different doses of rasagiline. My assessment of the results of orthostatic VS will not be provided in this review but will need to be presented in a separate review. Although these data were not collected under double-blinded conditions with a placebo group and a many different times throughout the dosing interval, review of these analyses might provide some insight into whether there are any effects of gender or age ("elderly" subjects > 65 years old vs "young" subjects 40-60 years old) on orthostatic VS.

3. Conclusions

The sponsor has satisfied PMC # to investigate orthostatic blood pressure and pulse timed to rasagiline dosing. This will be evaluated in both the tyramine challenge study and in the dose proportionality study.

4. Comments to Sponsor

The sponsor should be notified that the DNP has determined that it has satisfied PMC # to investigate orthostatic blood pressure and pulse timed to rasagiline dosing in the tyramine challenge study and in the dose proportionality study.

Leonard Peter Kapcala, M.D.
Medical Reviewer

Gerald Podskalny, D.O.
Team Leader, DNP

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21641	PMR/PMC 1	TEVA NEUROSCIENCE INC	AZILECT (RASAGILINE MESYLATE) 1MG TABLET
NDA 21641	SUPPL 8	TEVA NEUROSCIENCE INC	AZILECT (RASAGILINE MESYLATE) 1MG TABLET

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/s/

LEONARD P KAPCALA
08/27/2009
Dave, Here is my PMC review. Please let me know if any questions. Thanx. Len

GERALD D PODSKALNY
08/31/2009