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APPLICATION NUMBER:

21-641/S-008

OFFICE DIRECTOR MEMO

MEMORANDUM

DATE: December 8, 2009

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-641

SUBJECT: Action Memo for NDA 21-641, to change the label for Azilect (rasagiline mesylate)

NDA 21-641, to change the label for Azilect (rasagiline mesylate), was submitted by TEVA Pharmaceuticals on 2/6/09 in fulfillment of several Phase 4 commitments. Specifically, at the time of the approval of Azilect, a monoamine oxidase Type B (MAO B) inhibitor approved as a treatment for Parkinson's Disease, there was insufficient evidence to establish that 1) it was selective for MAO B, and 2) it had no appreciable MAO A inhibitory activity. Drugs that have significant MAO A inhibitory activity can result in hypertensive crises in the presence of (sufficient amounts) of dietary tyramine. Because of the uncertainty about Azilect's MAO A inhibitory activity, Azilect was approved with labeling requiring restrictions on dietary tyramine. We required the sponsor to perform an adequate study in Phase 4 to definitively establish whether or not at the recommended dose of Azilect (1 mg/day) there was a significant hypertensive effect in the presence of dietary tyramine. In addition, the sponsor was required to perform a study to determine the effect on the bioavailability of tyramine from a tyramine-rich meal. In this application, the sponsor has submitted the results of these required studies.

The application has been reviewed by Dr. Leonard Kapcala, medical officer, Dr. Hristina Dimova, Office of Clinical Pharmacology, and Dr. David Podskalny, neurology team leader.

Dr. Kapcala has performed an extensive and detailed review of Study TVP-1012-120-TYR, the tyramine sensitivity study. He has concluded that, at the recommended dose of 1 mg/day, Azilect demonstrates some increased sensitivity to exogenous tyramine. That is, at 1 mg/day of Azilect, in the presence of relatively high doses of tyramine, there is an increased incidence of hypertensive responses compared to placebo. This establishes that Azilect is not completely selective for MAO B, even at the recommended dose. However, with increasing doses of Azilect, smaller doses of tyramine produce a hypertensive response, and, at the recommended dose of 1 mg/day, there is little risk of hypertensive crises, given the typical amounts of tyramine present in most meals. Of interest, in this study, selegiline, at the approved dose of 20 mg/day, demonstrated a degree of tyramine sensitivity very similar to that for Azilect 1 mg/day; currently, selegiline labeling contains no dietary restrictions.

Given the results in this study, the team and I agree that the current labeling should be extensively revised, to remove the language requiring dietary tyramine restrictions. The labeling should describe the slight increased tyramine sensitivity even at the recommended daily dose, and should warn that very high levels of dietary tyramine may result in hypertensive crises even at this dose.

Dr. Dimova has reviewed the study to assess the bioavailability of capsules of tyramine with and without food, and a tyramine rich meal. She notes a decreased bioavailability of the tyramine capsules when taken with food compared to when they are taken without food, and also a decrease in the bioavailability of tyramine when given as a tyramine rich meal compared to a similar amount of tyramine when given as capsules. These data were deemed important to help understand previously performed tyramine sensitivity studies as well as to gain an understanding of what actual hypertensive responses to tyramine rich foods might be, compared to the responses seen in the formal tyramine sensitivity study described above, in which tyramine was given as capsules.

For the reasons described above, then, we have extensively revised labeling, and have agreed with the sponsor on this revised label. Therefore, I will issue the attached Approval letter, with revised labeling. This label also includes language related to several labeling supplements submitted by the sponsor (see Dr. Podskalny's review for the details of these supplements).

Russell Katz, M.D.

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

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/s/

RUSSELL G KATZ
12/09/2009