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APPLICATION NUMBER:

NDA 21-894

SUMMARY REVIEW

MEMORANDUM

DATE: August 8, 2008

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-894

SUBJECT: Approval Memo for NDA 21-894, for the use of Xenazine (tetrabenazine) in the treatment of the chorea of Huntington's Disease

NDA 21-894, for the use of Xenazine (tetrabenazine) in the treatment of the chorea of Huntington's Disease, was submitted by Prestwick Pharmaceuticals on 4/22/05, subsequently withdrawn, and resubmitted on 9/26/05. The Agency has issued three previous Approvable letters: on 3/24/06, 12/26/07, and 3/18/08. In addition, this application was discussed at a meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee (PCNS AC) on 12/6/07. Our various reviews and the discussion of the PCNS AC identified several areas of concern, including the potential for tetrabenazine to cause depression and possible decrements in cognitive functioning. Despite these concerns, the AC voted overwhelmingly to recommend approval of the application.

Based on our reviews and discussions, we agreed that the application should be approved with a Risk Evaluation and Mitigation Strategy (REMS) in place to ensure the safe use of the product. The primary issues that we concluded necessitated the adoption of a REMS included concerns about depression and possible important drug-drug interactions related to the fact that tetrabenazine is metabolized by CYP2D6. Careful dose titration is required to address these issues (as well as close clinical monitoring), and comprehensive educational efforts were felt to be necessary to ensure proper use of the drug (for a detailed discussion of the data and issues identified prior to the most recent Approval letter, see my memo of 3/17/08).

In the most recent Approvable letter (3/18/08), the Agency asked the sponsor to adopt our proposed labeling and Medication Guide, and to submit a revised REMS. The sponsor has responded to this letter in a submission dated 6/16/08. This response has been reviewed by Dr. Lourdes Villalba, division safety reviewer, Dr. Laura Pincock of the Office of Surveillance and Epidemiology (OSE), the OSE Tetrabenazine Risk Management Team, and Dr. Sripal R. Mada, Office of Clinical Pharmacology. Based on the reviews of this and subsequent submissions, as well as numerous telephone conferences with the sponsor, the sponsor and the Agency have agreed to the following documents:

- 1) product labeling
- 2) REMS Elements
 - a. Medication Guide
 - b. Pharmacist materials
 - i. Dear Pharmacist letter
 - ii. Package Insert
 - iii. Medication Guide
 - iv. A Healthcare Professional Guide
 - c. Prescriber materials
 - i. Package Insert
 - ii. Dear Healthcare Provider letter
 - iii. Medication Guide
 - iv. A Healthcare Provider Professional Guide
 - v. A Patient/Caregiver Counseling Guide
 - vi. Initial Dosing Plan
 - d. Plans to notify pharmacies about the risks of tetrabenazine
 - e. Plans for on-going Healthcare Professional Education
 - f. Plans for distributing REMS materials to physicians and pharmacists
 - g. Plans for periodically assessing the success of the REMS (specific documents/surveys to be submitted at least 2 months before their planned use)

The specific documents and detail of the plans referenced above are included as an attachment to the proposed Approval letter. As noted, the primary issues addressed in these documents are the potential for tetrabenazine to cause depression, and the potential for drug-drug interactions and other toxicity related to the fact that tetrabenazine is a substrate for CYP2D6 (for example, because we have little clinical experience with doses of tetrabenazine effectively above 100 mg/day, we have imposed a requirement that if a daily dose of greater than 50 mg is contemplated, patients should be genotyped; doses greater than 50 mg/day are not recommended for poor metabolizers). Also as noted above, the sponsor and we have agreed to the necessity of the REMS, the specific documents to be included, and the specific language in all of the documents described above.

Finally, the attached Approval letter describes the following post-marketing required studies (to which the sponsor has committed):

- 1) Complete the 2 year carcinogenicity study in male rats
- 2) Conduct a 2 year carcinogenicity study in female rats
- 3) Conduct a non-clinical reproductive toxicity study
- 4) Submit in vivo metabolism data in the species used in the non-clinical studies (particularly the reproductive toxicology and carcinogenicity studies)

- 5) Conduct a neurotoxicity study
- 6) Conduct an in vitro metabolism study

Given that we have agreed with the sponsor on the specific elements of the REMS, the language of the product labeling, and the requirements for the post-marketing studies described, we recommend that the Application be approved, and that the attached Approval letter and appended documents be issued.

**APPEARS THIS WAY
ON ORIGINAL**

Risk Evaluation and Mitigation Strategy (REMS) Requirements –XENAZINE (tetrabenazine) Tablets

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- (F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of XENAZINE outweigh its risks. In reaching this determination, we considered the following:

- A. While it is not possible to estimate the size of the population likely to use XENAZINE, the number of patients affected with Huntington's disease in the United States is approximately 30,000.
- B. XENAZINE will be approved to treat the chorea of Huntington's disease, a serious medical condition. Chorea, a motor disorder characterized by involuntary movements, can impact a patient's ability to carry out activities of daily living. It also can be a contributor to falls, associated injuries, and institutionalization.
- C. XENAZINE has been shown to reduce the chorea of Huntington's disease.
- D. We expect that tetrabenazine would be chronic therapy for patients for whom it is effective without intolerable side effects.
- E. Known serious risks associated with use of XENAZINE include the occurrence of depression and suicidality, and neuroleptic malignant syndrome (NMS). In a controlled clinical trial in Huntington's disease, depression occurred in 19% of 54 XENAZINE-treated patients as compared to 0% of 30 patients on placebo treatment. One patient committed suicide and one had suicidal ideation in the XENAZINE-treated group, and no patient had such events in the placebo-treated group. Although no cases of NMS occurred in the controlled clinical trial with XENAZINE, cases of NMS have been reported in the foreign postmarketing setting prior to US approval. Other important risks associated with XENAZINE include but are not limited to akathisia, parkinsonism, and QT prolongation. Akathisia and parkinsonism may be difficult to distinguish from the underlying disease. In the controlled trial mentioned above, akathisia was observed in 19% of patients randomized to XENAZINE and no patients randomized to placebo. Parkinsonism and other extrapyramidal events were observed in 15% of patients randomized to XENAZINE and no patients randomized to placebo. XENAZINE causes a small increase (about 8 msec) in the corrected QT (QTc) interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases.
- F. XENAZINE is a new molecular entity (NME).

In addition, pursuant to 21 CFR Part 208, FDA has determined that XENAZINE poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of XENAZINE. FDA has determined that XENAZINE is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use XENAZINE. In addition, patient labeling could help prevent serious adverse effects related to the use of the product.

The elements of the REMS will include prescriber, pharmacist and patient/caregiver educational materials (including but not limited to a Medication Guide, a Prescriber Patient/Caregiver Counseling Guide, a Dear Doctor Letter, a Dear Pharmacist Letter, a Healthcare Professional Guide and an Initial Dosing Plan Card) and a timetable for submission of assessments of the REMS.

**APPEARS THIS WAY
ON ORIGINAL**