NDA 21-894 Xenazine® (tetrabenazine)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

To reduce the risk of drug-associated depression and suicidality in patients receiving Xenazine® (tetrabenazine), to promote informed prescribing and proper titration and dosing of tetrabenazine, and to minimize the risk of drug-drug interactions with strong CYP2D6 inhibitors.

II. REMS ELEMENTS

A. Medication Guide

In compliance with 21 CFR 208.24, Biovail will institute the following measures:

- A Medication Guide will be dispensed with each tetrabenazine prescription.
- Three (3) Medication Guides will be attached to each Xenazine package.
- The package will also include a prominent notice to include a Medication Guide with each prescription in the event that less than a full bottle of Xenazine is prescribed.
- The "Dear Pharmacist" letter will include instructions to provide the Medication Guide with each prescription.
- Ten (10) Medication Guides will be included with the "Dear Pharmacist" letter.
- Medication Guides will be available via sales and/or clinical representatives, the product website or through the Sponsor toll-free medical information line.

B. Communication Plan

Biovail will implement a communication plan to healthcare providers to support implementation of this REMS:

1. The audience is healthcare professionals (HCPs)—especially neurologists and movement disorder specialists and pharmacists.
2. Biovail will provide physicians and pharmacists with the educational materials listed below that describe the key risks and benefits of tetrabenazine:

    a. Prescriber materials:
        i. Xenazine® Package Insert (PI)
        ii. Dear Healthcare Professional Letter
        iii. Xenazine® Medication Guide
        iv. Prescribing Xenazine®: A Healthcare Professional Guide
        v. Patient/Caregiver Counseling Guide

vi. Initial Dosing Plan

b. Pharmacist materials
   i. Dear Pharmacist Letter
   ii. Xenazine® Package Insert (PI)
   iii. Xenazine® Medication Guide
   iv. Prescribing Xenazine®: A Healthcare Professional Guide

c. All final communication and educational materials listed above are appended to the REMS.

3. Pharmacy Management Systems - Biovail will work with First Data Bank, MediSpan, Facts and Comparisons, Micromedex, major pharmacy benefit managers and other leading providers of point of sale clinical alert data to inform dispensing pharmacists and pharmacy technicians of the significant known risks of tetrabenazine. In working with these data providers, Biovail will seek to include appropriate drug-drug interaction information, dosing guidelines and other clinical alerts available to it through the use of standard NCPDP data formats.

4. Ongoing Healthcare Professional Education - The Sponsor will also use several educational vehicles to continue educating and updating Healthcare Professionals about tetrabenazine and the REMS. These include a trained Speaker's Bureau which will schedule local and regional thought leader symposia. The speaker materials will include information on the tetrabenazine REMS and will be used to reinforce the risk minimization messages after launch. The Sponsor's clinical team and sales professionals will be present at annual meetings of the major professional societies of neurologists and movement disorder specialists (e.g., American Academy of Neurology, American Neurological Association, Movement Disorder Society) and will use these opportunities to reinforce the REMS messages. Continuing education formats will also be available for physicians and pharmacists on the product web site.

5. Distribution of materials:
   a. At the time of tetrabenazine availability, the Dear Healthcare Professional Letter will be sent by mass mailing to targeted medical specialists to announce the availability of tetrabenazine and to educate them on proper patient selection and use of the drug. The mailing will also include a copy of the PI, the *Prescribing Xenazine®: A Healthcare Professional Guide*, the patient Medication Guide, the *Patient/Caregiver Counseling Guide* and the Initial Dosing Plan (as described above). Additional materials will be available via sales and/or clinical representatives, the product website or through the Sponsor toll-free medical information line.
   b. At the time of tetrabenazine availability, a letter will be sent by mass mailing to pharmacists who dispense tetrabenazine through specialty pharmacies to announce the availability of tetrabenazine and to educate pharmacists on the tetrabenazine REMS. The mailing will also include a copy of the PI and the *Prescribing Xenazine®: A Healthcare Professional Guide*. Pharmacists will also be provided with 10 copies of the Medication Guide. The pharmacist can obtain additional educational materials from the Sponsor toll-free medical information line or the product website.

c. In order to ensure that healthcare professionals remain informed of the tetrabenazine REMS, the Dear Healthcare Professional letter and the Dear Pharmacist letter will be updated annually for the next five years and sent to all neurologists, movement disorder specialists and pharmacists. These annual mailings will include the most current PI, *Prescribing Xenazine®: A Healthcare Professional Guide*, *What You Need to Know About Xenazine®: Patient/Caregiver Counseling Guide*, and Medication Guide.

C. Elements To Assure Safe Use

Tetrabenazine has been shown to be effective but is associated with risk of depression and suicidality. Tetrabenazine can be approved without any elements to assure safe use.

D. Implementation System

Because tetrabenazine can be approved without any elements to assure safe use, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to FDA no less frequently than at 18 months, 3 years, and 7 years after approval (August 15, 2008). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The assessment is to be received by the US Food and Drug Administration (FDA) on or before the due date.