



NDA 21894/S-005

**SUPPLEMENT APPROVAL**

Biovail Americas Corporation  
Attention: James H. Medley, Ph.D. Vice President, Regulatory Affairs  
700 Route 202/206 North  
Bridgewater, NJ 08807

Dear Dr Medley:

Please refer to your Supplemental New Drug Application (sNDA) dated July 28, 2010, received July 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xenazine (tetrabenazine) Tablets.

We acknowledge receipt of your amendments dated February 8, 17, and 28, 2011 and your risk evaluation and mitigation strategy (REMS) assessment dated December 23, 2009, received December 28, 2009.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Medication Guide), with the addition of any labeling changes in pending "Changes Being Effectuated" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Xenazine (tetrabenazine) was originally approved on August 15, 2008, and a REMS modification was approved on December 1, 2009. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS include revisions to the goals, and revised Medication Guide and communication plan materials to improve understanding by patients and healthcare professionals of the key risk messages of the Xenazine (tetrabenazine) REMS.

Your proposed modified REMS, submitted on February 17, 2010, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on August 15, 2008.

The revised REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of patients' understanding of the serious risks of tetrabenazine, the importance of titration, and monitoring for targeted adverse events.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
4. Surveys designed to monitor the effectiveness of the interventions in educating prescribers on the proper use of tetrabenazine therapy, compliance with the titration and dosing guidelines contained in the labeling, and occurrence of targeted adverse events and their management by the prescriber.
5. For the Pharmacy Management Systems section of the Communication Plan:

- a. A summary of the activities completed with the Pharmacy Management Systems under Section B3 of the REMS. Please include copies of any materials or screen shots that were developed and used.
  - b. The number and percentage of US pharmacies that were reached through the Pharmacy Management Systems described in item B3 of the REMS. Include a general description of pharmacies that are not covered by these Pharmacy Management Systems (for example: independents, rural etc.).
4. For the Ongoing Healthcare Professional Education section, the number of unique healthcare professionals who participated in thought leader symposia, by calendar quarter, since the inception of the REMS program.
5. For the Distribution of Materials section:
  - a. The source(s) of the list of physician addresses
  - b. The source(s) of the list of pharmacist addresses
  - c. The date(s) of each mailing
  - d. The number of recipients at each mailing date
  - e. The number of returned mailings for each date
  - f. A list of the documents included in each mailing
6. Based on the results of the surveys and any other relevant information, an assessment and conclusion whether the REMS is meeting its goals and whether modifications to the REMS are needed.
7. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 021894 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 021894  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 021894  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any

new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Beverly Conner, Regulatory Project Manager, at (301) 796-1171.

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

ENCLOSURES:  
Content of Labeling  
REMS

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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.**  
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/s/  
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RUSSELL G KATZ  
05/04/2011