DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021894/S-004

SUPPLEMENT APPROVAL

Valeant Pharmaceutical North America LLC
C/O Valeant International SRL
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 November 13, 2009, received November 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xenazine (tetrabenazine) Tablets.

We acknowledge receipt of your amendment dated May 26, 2011.

This "Prior Approval" supplemental new drug application provides for label reformatting per the Physician's Labeling Rule.

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.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (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).

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Xenazine was approved on August 15, 2008, we have become aware of a new major circulating human metabolite, 9-desmethyl-β-DHTBZ, identified in a post-approval study you submitted on May 27, 2009. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risks of drug interactions due to induction or inhibition of CYP450 enzymes by 9-desmethyl-β-DHTBZ, drug interactions due to inhibition of P-glycoprotein by 9-desmethyl-β-DHTBZ, the unexpected serious risks of adverse effects on embryo-fetal and pre- and postnatal development, of mutagenicity and carcinogenicity, and the unexpected serious risks resulting from unanticipated binding of 9-desmethyl-β-DHTBZ to specific receptors.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1790-1 An *in vitro* study to evaluate the potential for 9-desmethyl-β-DHTBZ to induce CYP450 enzymes, based on the FDA guidance "Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2011
Study Completion:	02/2012
Final Report Submission:	04/2012

1790-2 An *in vitro* study to evaluate the potential for 9-desmethyl-β-DHTBZ to inhibit CYP450 enzymes, based on the FDA guidance "Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2011
Study Completion:	02/2012
Final Report Submission:	04/2012

1790-3 An *in vitro* study to evaluate the potential for 9-desmethyl-β-DHTBZ to inhibit P-glycoprotein, based on the FDA guidance "Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2011
Study Completion:	03/2012
Final Report Submission:	05/2012

1790-4 A study to determine the feasibility of conducting nonclinical (embryo-fetal development, prenatal and postnatal development, carcinogenicity) studies to assess the potential toxicity of 9-desmethyl-β-dihydrotetrabenazine (1-O-dealkyl DHTBZ, RUS0893). This would entail identifying one or more animal species in which plasma levels of DHTBZ can be achieved (for a sufficient duration) that are similar to or exceed plasma levels observed in humans at the clinically relevant doses of tetrabenazine.

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2011
Study Completion:	04/2012
Final Report Submission:	06/2012

1790-5 A prenatal and postnatal development (including maternal function) study of 9-desmethyl-β-dihydrotetrabenazine (1-O-dealkyl DHTBZ, RUS0893) in a rodent species in which plasma levels can be achieved that are similar to or greater than plasma levels in humans at clinically relevant doses of tetrabenazine.

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2013
Study Completion:	10/2013
Final Report Submission:	02/2014

1790-6 An *in vitro* bacterial reverse mutation (Ames) assay (including human hepatic S9 metabolic activation system) on the main circulating human metabolite of tetrabenazine, 9-desmethyl-β-dihydrotetrabenazine (1-O-dealkyl DHTBZ, RUS0893).

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2012
Study Completion:	08/2012
Final Report Submission:	10/2012

1790-7 A carcinogenicity study in one animal species in which plasma levels of 9-desmethyl-β-dihydrotetrabenazine can be achieved that are similar to or greater than plasma levels in humans at clinically relevant doses of tetrabenazine.

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2013
Study Completion:	12/2013
Final Report Submission:	04/2014

1790-8 An embryo-fetal development study of 9-desmethyl-β-dihydrotetrabenazine (1-O-dealkyl DHTBZ, RUS0893) in an animal species in which plasma levels can be achieved that are similar to or greater than plasma levels in humans at clinically relevant doses of tetrabenazine.

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2013
Study Completion:	10/2013
Final Report Submission:	02/2014

1790-9 An *in vitro* chromosomal aberration assay (including human hepatic S9 metabolic activation system) on the main circulating human metabolite of tetrabenazine, 9-desmethyl-β-dihydrotetrabenazine (1-O-dealkyl DHTBZ, RUS0893).

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2012
Study Completion:	08/2012
Final Report Submission:	10/2012

1790-10 A comprehensive panel of *in vitro* receptor-binding assays to determine the pharmacological target(s) of the main circulating human metabolite of tetrabenazine, 9-desmethyl-β-dihydrotetrabenazine (1-O-dealkyl DHTBZ, RUS0893).

The timetable you submitted on June 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2011
Study Completion:	02/2012
Final Report Submission:	04/2012

Submit the protocols to your IND 063909 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify each submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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.

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, Pharm.D., 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

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
07/06/2011