

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022345Orig1s000**

**OTHER ACTION LETTERS**



NDA 022345

**COMPLETE RESPONSE**

Valeant Pharmaceuticals North America  
Attention: Susan T. Hall, Ph.D.  
Head of Neurology R&D and Regulatory Compliance  
280 S. Magnum Street, Suite 210  
Durham, NC 27701

Dear Dr. Hall:

Please refer to your New Drug Application (NDA) dated October 30, 2009, received October 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for POTIGA (ezogabine) tablets, 50 mg, (b) (4), 200 mg, 300 mg, 400 mg.

We acknowledge receipt of your amendments dated: November 19, 2009; November 20, 2009; December 4, 2009; December 8, 2009; December 11, 2009; December 24, 2009; January 26, 2010; February 12, 2010; February 17, 2010; February 26, 2010; March 4, 2010; March 5, 2010 (2); March 11, 2010; March 12, 2010; March 24, 2010; April 1, 2010, April 9, 2010 (2); April 21, 2010; May 11, 2010; May 14, 2010; May 20, 2010; June 4, 2010; June 21, 2010; July 6, 2010; July 9, 2010; July 19, 2010; July 20, 2010; July 26, 2010; July 29, 2010; August 26, 2010; August 27, 2010; October 8, 2010; October 18, 2010; October 20, 2010; October 22, 2010; November 15, 2010; November 17, 2010.

We also acknowledge receipt of your amendment dated August 26, 2010, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**NONCLINICAL**

The NDA is not approvable due to the high specification limit proposed for the mutagenic impurity (b) (4)

(b) (4) was reproducibly positive in the Ames assay, both in the presence and absence of metabolic activation. Although (b) (4) was negative when tested *in vivo* in a combined rat micronucleus and Comet assay, we believe these results do not provide a basis for dismissing the mutagenic potential clearly demonstrated in the Ames assay. The Ames assay and the *in vivo* assays evaluate different genotoxicity endpoints that do not always correlate and, at this time, there are inadequate data to determine whether a negative Comet assay has adequate negative

predictive value to provide reassurance in the face of a positive Ames test. An earlier effort to establish a higher Threshold of Toxicological Concern for (b) (4) based on an assessment of the structure-activity relationship (b) (4)

(b) (4) was considered inadequate, because it relied on several unsubstantiated assumptions, in particular, that published carcinogenicity data on structurally related compounds accurately reflect the carcinogenic potential of (b) (4), and that doses of structurally related compounds can be extrapolated to (b) (4). Therefore, you will need to lower the specification limit to one that results in a daily dose of (b) (4) considered acceptable for a genotoxic impurity (for ezogabine at proposed doses, (b) (4))

## **BIOPHARMACEUTICS**

(b) (4)

## **LABELING**

We are including our revised version of the draft labeling. We ask that you submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, using our revised labeling as the base document, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

In addition, we have completed our review of your carton and container labeling submitted on October 8, 2010 and have no further comments at this time. As part of your response to this letter, we ask that you resubmit draft carton and container labeling in order to facilitate review of your resubmission.

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

As described in our letter dated August 16, 2010, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for POTIGA to ensure that the benefits of the drug outweigh the risk(s) of 1) suicidal thoughts and behavior associated with the class of antiepileptic drugs (AEDs), of which POTIGA (ezogabine) is a member and 2) urinary retention and its associated morbidities.

We note that your August 26, 2010, amendment contained a response to our August 16, 2010, letter; as noted above, this amendment was not reviewed for this action. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

## **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

### **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Stephanie N. Keefe, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{ See appended electronic signature page }

Ellis F. Unger, M.D.  
Deputy Director  
Office of Drug Evaluation I  
Office of New Drugs  
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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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ELLIS F UNGER  
11/30/2010