DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022345

NDA APPROVAL

Valeant Pharmaceuticals North America
Attention: Charity Abelardo, RAC
280 S. Mangum Street, Suite 210
Durham, NC 27701

Dear Ms. Abelardo:

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 (FDCA) for Potiga (ezogabine) Tablets, 50mg, 200mg, 300mg, and 400 mg.

We acknowledge receipt of your amendments dated April 15 and 21, and June 10, 2011.

The April 15, 2011, submission constituted a complete response to our November 30, 2010, action letter.

This new drug application provides for the use of Potiga as adjunctive treatment for adult patients with partial-onset seizures with or without secondary generalization.

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

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you that on June 21, 2010, you agreed not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when finalized, appropriate revisions will be made to the package insert, the Medication Guide and the container and carton labels through supplementation of your NDA. This would include the statements detailing the scheduling of Potiga in the labeling, as required under 21 CFR 201.57(c)(10)(i).

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). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and the carton and immediate container labels submitted on June 10, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022345**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages zero to 4 weeks of age because the necessary studies are impossible or highly impracticable. This is because there are too few children with this condition to study.

We are deferring submission of your pediatric studies for ages one month to 11 years of age because pediatric studies should be delayed until additional safety and effectiveness data have been collected in an older pediatric age group (12 to 16 years old). We are deferring submission of your pediatric studies for ages 12 to 16 years of age because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1781-1 Conduct a prospective, randomized, placebo-control, double-blinded efficacy/safety trial of Potiga (ezogabine) in children ≥12 years old.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2012
Trial Completion:	01/2018
Final Report Submission:	05/2018

1781-2 Conduct a long-term open label extension study of ezogabine in children ≥12 years old.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2011
Study Completion:	07/2019
Final Report Submission:	11/2019

Reports of these required pediatric postmarketing studies must be submitted as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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.

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 assess a known serious risk of urinary retention; to identify an unexpected serious risk of drug interactions between ezogabine and drugs that inhibit or induce transporters in the kidney if ezogabine is a substrate for the transporters; to identify an unexpected serious risk of the potential for drug interactions due to inhibition of CYP2B6 by ezogabine when available data indicate the potential for a serious risk; or to identify an unexpected serious risk of the potential for chronic administration of ezogabine to produce a withdrawal syndrome following drug discontinuation.

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 these serious risks.

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

1781-3 A prospective cohort study to better define the risk of urinary retention in patients with epilepsy treated with ezogabine and how the risk may vary with demographics (e.g. age), comorbidities that influence voiding (e.g., benign prostatic hyperplasia [BPH], multiple sclerosis) and concomitant medications that may influence voiding. The study will be performed utilizing a research database to compare patients started in two cohorts, those started on ezogabine with those started on other anticonvulsants, for the incidence of urinary retention. The study will analyze approximately 2,000 to 4,000 ezogabine-exposed patients.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2012
Study Completion:	09/2014
Final Report Submission:	11/2014

1781-4 An *in vitro* study to evaluate whether ezogabine is a substrate for major transporters in the kidney. Refer to the Agency's Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf) for more detailed recommendations regarding transporter-based drug-drug interactions.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2011
Study Completion:	10/2011
Final Report Submission:	11/2011

1781-5 An *in vitro* study to evaluate the potential for ezogabine to inhibit CYP2B6.

The timetable you submitted on June 2, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2011
Study Completion:	10/2011
Final Report Submission:	11/2011

1781-6 An animal physical dependence study to evaluate whether chronic administration of ezogabine produces a withdrawal syndrome following drug discontinuation. Refer to the “Guidance for Industry: Assessment of Abuse Potential of Drugs" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf for information about how to design abuse-related studies, including a physical dependence study.

The timetable you submitted on June 6. 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2011
Study Completion:	01/2012
Final Report Submission:	05/2012

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the mechanism for a known serious risk of urinary retention or to identify an unexpected serious risk for drug interaction with P-glycoprotein substrates when available data indicate the potential for a serious risk.

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

1781-7 A controlled urodynamic trial, to include adults of both sexes in a wide range of ages, including the elderly. Pre- and post-drug urodynamic measures should be carefully collected. Urodynamic measurements should include, although not necessarily be limited to, uroflowmetry, multichannel cystometry, electromyography (EMG), and subjective sensory reporting.

The timetable you submitted on June 2, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/2012
Study Completion:	07/2015
Final Report Submission:	11/2015

1781-8 A clinical trial to evaluate the acetyl metabolite of ezogabine (NAMR) as an inhibitor of P-glycoprotein using digoxin as a probe substrate. Refer to the Agency's Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf) for more detailed recommendations regarding transporter-based drug-drug interactions.

Final Protocol Submission:	11/2011
Trial Completion:	04/2012
Final Report Submission:	08/2012

Submit the draft protocols approximately 45 days in advance of the final protocol submission dates to allow for Agency review and comment.

Submit the protocols and amendments to your IND 053950 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letters dated August 16, 2010 and May 25, 2011.

Your proposed REMS, submitted on June 9, 2011, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

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

a. An evaluation of prescribers' and pharmacists' understanding of the serious risks of Potiga (ezogabine)
b. Date of retail availability of Potiga
c. Sources of lists of prescriber and pharmacist addresses
d. Date(s) of distribution
e. Method of distribution (e.g., mail, email, contract carrier, etc.)
f. Number of recipients on each distribution list

g. Number of documents returned (undelivered)
h. List of all documents included in each distribution
i. 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.

We remind you that 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 the FDCA.

If you 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 with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022345 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022345
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022345
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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see 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).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Stephanie 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
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
- Carton and Container Labeling
- REMS
- REMS Materials

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

/s/

ELLIS F UNGER
06/10/2011