

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022345Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022345

SUPPL #

HFD # 120

Trade Name Potiga

Generic Name ezogabine

Applicant Name Valeant Pharmaceutical North America, Inc.

Approval Date, If Known June 10, 2011

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:



Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

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Name of person completing form: Karen Abraham-Burrell, Pharm.D.  
Title: Regulatory Project Manager  
Date: June 7, 2011

Name of Office/Division Director signing form: Russell Katz, MD  
Title: Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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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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KAREN D ABRAHAM-BURRELL  
06/07/2011

RUSSELL G KATZ  
06/10/2011

**CONFIDENTIAL**

m1.3.3 Debarment Certification

## **DEBARMENT CERTIFICATION**

Valeant Pharmaceuticals certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 022345).



Dr. Sue Hall

October 2009

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 022345 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Potiga Established/Proper Name: ezogabine Dosage Form: tablets		Applicant: Valeant Pharmaceuticals North America Agent for Applicant (if applicable): Susan Hall, Ph.D. / Charity Abelardo
RPM: Stephanie Keefe Karen Abraham-Burrell (acting 4/25-11 – 6/10/11)		Division: DNP
<p><b>NDAs:</b> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: [N/A] Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>June 15, 2011</u></li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  <input checked="" type="checkbox"/> Complete Response 11/30/10
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input checked="" type="checkbox"/> N/A

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics <sup>2</sup>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority          Chemical classification (new NDAs only): 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input checked="" type="checkbox"/> N/A
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input checked="" type="checkbox"/> N/A
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action (Wei Lu)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP) (Sandy Walsh)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input checked="" type="checkbox"/> No
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

N/A

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

N/A

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

N/A

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

N/A

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input checked="" type="checkbox"/> N/A</p>
<p><b>CONTENTS OF ACTION PACKAGE</b></p>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	
<p><b>[Tab A] Officer/Employee List</b></p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p><b>[Tab B] Action Letters</b></p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Approval Letter 06/10/11 Complete Response 11/30/10 Complete Response Resubmission 04/15/11</p>
<p><b>[Tab C] Labeling</b></p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	<p>June 3, 2011 / June 8, 2011</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>October 30, 2009</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 6/18/10

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	See Labeling Section C
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	See Labeling Section C
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	See Labeling Section C
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	July 26, 2010
<ul style="list-style-type: none"> <li>❖ Proprietary Name                     <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	Letter date: 2/18/10 Review date: 2/18/10 DMEPA 7/28/10, 11/10/10
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> DMEPA 8/13/10, 11/10/10 <input checked="" type="checkbox"/> DRISK 10/14/10 <input checked="" type="checkbox"/> DDMAC 12/17/10 <input checked="" type="checkbox"/> CSS (see tab F) <input checked="" type="checkbox"/> SEALD 06/10/11 Meetings 5/9/11, 5/16/11, 5/23/11, 6/3/11, 6/6/11, 6/7/11, 6/9/11
<b>[Tab D] Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	CMC Filing Review 11/19/09 Non-Clinical Filing Review 12/15/09 RPM Filing Review 1/28/10 Clinical Pharmacology Filing Review 11/18/10  <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP                     <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No N/A N/A <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)                     <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>August 18, 2010</u>                              If PeRC review not necessary, explain: <u>N/A</u></li> <li>• Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<p>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i></p>	<p><input checked="" type="checkbox"/> Verified, statement is acceptable</p>
<p>❖ Outgoing communications <i>(letters (except action letters), emails, faxes, telecons)</i></p>	<p>NDA Acknowledgement 11/12/09            QT/IRT Info Request 11/12/09            Administrative Info Request 11/12/09            Statistics Info Request 11/24/09            General Advice Letter 12/22/09            Clinical Info Request 12/22/09            Mtg Request Denied 12/23/09            Filing Issues Identified 1/12/10            Clinical Info Request 1/14/10            QT/IRT Info Request 2/16/10            Proprietary Name Granted 2/18/10            Clinical Info Request 3/31/10            CMC Info Request 5/3/10            CMC Info Request 5/28/10            Statistical Info Request 6/22/10            CSS Info Requests 6/22/10            Clinical Info Requests 6/22/10            Clin/Pharm Info Request 6/22/10            Urology Info Request 6/22/10            Non-Clinical Info Request 6/22/10            Clinical Info Request 6/22/10            CMC Info Request 6/25/10            Clinical Info Request 6/28/10            Clinical Info Request 7/8/10            CSS Info Request 7/13/10            Change of Applicant Address 8/16/10            CMC Info Request 8/16/10            Review Extension – Major Amendment 8/30/10            DMEPA Info Request 9/30/10            Clinical Info Request 11/4/10            Acknowledge Class 1 Resubmission – 04/26/11            e-mail communication –various dates            REMS Element Retraction Letter – 05/25/11            REMS Element Retraction Memo – 05/26/11            REMS amendment 06/06/2011            NDA Advise Letter 06/14/11</p>
<p>❖ Internal memoranda, telecons, etc.</p>	<p>Statistics Consult 11/4/09            CAC Consult 11/5/09            Statistics Consult 11/12/09            Cardio-Renal Consult 11/12/09            CSS Consult 11/13/09            DMEPA Consult 11/20/09            DRISK Consult 12/4/09            Urology Consult 12/17/09            Abuse Liability Consult 12/18/09            DSI Clinical Consult 01/4/10            DDMAC Consult 01/19/10            DSI Clinical Consult 6/28/10</p>

	DSI Biopharm Consult 8/19/10 Information Advisory 06/1/11
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	10/11/07 and 8/31/09
• EOP2 meeting ( <i>indicate date of mtg</i> )	12/8/04
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	EOP2 CMC: 10/25/04 SPA meetings: 12/16/02; 6/3/04; 6/29/05; 8/18/05
❖ Advisory Committee Meeting(s)	
• Date(s) of Meeting(s)	August 11, 2010
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	September 2, 2010 (Min. dated 8/11/10)
<b>[Tab E] Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 11/30/10 & 06/10/11
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 11/29/10 & 06/09/11
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 11/30/10 & 06/09/11
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> 06/09/11
<b>[Tab F] Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See CDTL Review in Tab E
• Clinical review(s) ( <i>indicate date for each review</i> )	11/30/10 & 06/08/11
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Urology (7/9/10 and 2/24/10) <input checked="" type="checkbox"/> OT/IRT (1/29/10)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> 6/30/10 Review; 06/07/11 Stat Review 4/23/10
❖ Risk Management	REMS documents: 8/26/10 REMS Memo: 8/16/10; 05/26/11 REMS Letter: 8/16/10; 05/25/11 <input checked="" type="checkbox"/> Defer Comment Memo: 11/10/10 OSE Review – 05/16/11 DRISK Review – 05/09/11 DRISK Interim Review – 05/31/11 OC Review – 06/01/11

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

	CSS Review – 06/07/11 DRISK Final Review – 06/10/11 REMS amendment documents: 06/06/11; 06/09/11
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> Review: 8/10/10 Letters to Investigators: 9/2/10 9/17/10 10/7/10 12/6/10 1/20/11 2/9/11
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>[Tab G] Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> See Statistical Review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> See Statistical Review
Statistical Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 7/7/10
<b>[Tab H] Clinical Pharmacology</b> <input type="checkbox"/> None	
Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> See Clinical Pharmacology Review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> See Clinical Pharmacology Review
Clinical Pharmacology review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 11/22/10; 1/25/11; 06/06/11
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> 8/25/10
<b>[Tab I] Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 11/30/10
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 11/30/10
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input checked="" type="checkbox"/> 11/30/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> 7/27/10 and 5/18/10
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> 7/27/10
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested

<b>[Tab J] Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> 11/29/10; 06/02/11
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> See Product quality review(s)
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> ONDQA Biopharm: 8/13/10 ONDQA review: 8/30/10 Addendum: 11/8/10
❖ Microbiology Reviews		
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		Refer to CMC Review 8/30/10
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup>)</i>		Date completed: 4/19/10 <b>EER printout in CMC Review dated 8/30/10</b> <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		
		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



**DEPARTMENT OF HEALTH AND HUMAN  
SERVICES**

---

**Food and Drug  
Administration Silver  
Spring MD 20993**

NDA 022345

**REMS ELEMENT RETRACTION**

Valeant Pharmaceuticals North America  
Attention: Charity Abelardo, RAC  
1280 S. Mangum Street, Suite 210 Durham, NC 27701

Dear Ms. Abelardo:

Please refer to your October 30, 2009, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Potiga (ezogabine) tablets.

In our letter dated August 16, 2010, we notified you that a risk evaluation and mitigation strategy (REMS) is required for Potiga (ezogabine) to ensure that the benefits of the drug outweigh the increased risk of suicidal thoughts and behavior associated with the class of antiepileptic drugs (AEDs), of which Potiga (ezogabine) is a member, and the increased risk of urinary retention and its associated morbidities. We indicated that your REMS must include a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

We are reviewing your proposed REMS as described in your August 26, 2010 submission. Although we continue to believe that a REMS is necessary to ensure that the benefits of Potiga (ezogabine) outweigh its risks, upon further consideration, we have determined that a Medication Guide is not necessary to ensure the benefits of the drug outweigh the risks described above because labeling and a REMS that includes a communication plan will be adequate to describe these serious risks. The Medication Guide will be part of the approved labeling and be subject to the requirements under 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Therefore, based on our current understanding of the risks of suicidal thoughts and behavior and urinary retention, we have determined that the REMS must include only the following: a communication plan and timetable for submission of assessments.

You should submit an amendment to the proposed REMS and REMS supporting document included in your August 26, 2010, submission that removes the Medication Guide, as it is no longer required. All changes to your August 26, 2010 submission should be marked and highlighted. In addition, you should submit clean copies of the revised REMS Document, REMS Supporting Document, and other REMS materials.

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission.

**NDA 022345**  
**PROPOSED REMS – AMENDMENT**

If you have any questions, call Karen Abraham-Burrell, Regulatory Project Manager, at (301) 301-796-2721.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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ELLIS F UNGER  
05/25/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>	
TO: Division of Drug Marketing, Advertising, and Communications HFD-42 <b>Attention: Quynh-Van Tran and Meeta Patel</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Division of Neurology Products</b>	
REQUEST DATE April 27, 2011	IND NO.	NDA/BLA NO. 022345	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) NME NDA resubmission
NAME OF DRUG Potiga (ezogabine) tablets	PRIORITY CONSIDERATION high	CLASSIFICATION OF DRUG AED	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) May 16, 2011
NAME OF FIRM: Valeant Pharmaceuticals North America		PDUFA Date: PDUFA goal date: June 15, 2011	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
<b>EDR link to submission:</b> The entire submission may be accessed at : <a href="\\CDSESUB1\EVSPROD\NDA022345\022345.ENX">\\CDSESUB1\EVSPROD\NDA022345\022345.ENX</a> . The Potiga working label is in the e-room and may be accessed at : <a href="\\Cdsesub1\evsprod\NDA022345\0041">\\Cdsesub1\evsprod\NDA022345\0041</a>			
<b>Please Note:</b> There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Please review and comment on the proposed label and Medication Guide contained in the Class I resubmission of NDA 022345 for Potiga received on April 15, 2011. The NDA has a proposed indication for use as adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has a PDUFA goal date of June 15, 2011. The entire submission may be accessed at : <a href="\\CDSESUB1\EVSPROD\NDA022345\022345.enx">\\CDSESUB1\EVSPROD\NDA022345\022345.enx</a> . Labeling meetings have been tentatively scheduled for May 9, 16, 23; June 3, 9, 13. The REMS will be retracted for this application. The label/MG submitted uses the label that was attached to the CR letter as the base document and provides Sponsor proposals for revision.			
SIGNATURE OF REQUESTER Karen Abraham-Burrell, Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-2721 Email: karen.abraham-burrell@fda.hhs.gov			

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/s/  
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KAREN D ABRAHAM-BURRELL  
04/28/2011

## REQUEST FOR CONSULTATION

TO (Office/Division): **HFD-009/Controlled Substances Staff**  
Attention: Corinne Moody/Sandra Saltz and Michael Klein

FROM (Name, Office/Division, and Phone Number of Requestor):  
Division of Neurology Products

DATE  
April 27, 2011

IND NO.

NDA NO.  
022345

TYPE OF DOCUMENT  
NME NDA resubmission

DATE OF DOCUMENT  
April 15, 2011

NAME OF DRUG  
Potiga (ezogabine) tablets

PRIORITY CONSIDERATION  
High

CLASSIFICATION OF DRUG  
AED

DESIRED COMPLETION DATE  
May 16, 2011

NAME OF FIRM: Valeant Pharmaceuticals North America

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Please review and comment on the proposed label and Medication Guide contained in the Class I resubmission of NDA 022345 for Potiga received on April 15, 2011 and provide guidance as needed for the scheduling process. The NDA has a proposed indication for use as adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has a PDUFA goal date of June 15, 2011. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA022345\022345.enx. The Potiga working label is in the e-room and may be accessed at : <\\Cdsesub1\evsprod\NDA022345\0041>

Please also participate in labeling meetings as needed. The label/MG submitted uses the label that was attached to the CR letter as the base document and provides Sponsor proposals for revision. Labeling meetings have been tentatively scheduled for May 9, 16, 23; June 3, 9, 13

SIGNATURE OF REQUESTOR  
Karen Abraham-Burrell, Regulatory Project Manager, DNP  
Food and Drug Administration  
Phone: 301-796-2721  
Email: karen.abraham-burrell@fda.hhs.gov

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

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/s/  
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KAREN D ABRAHAM-BURRELL  
04/28/2011



NDA 022345

**ACKNOWLEDGE --  
CLASS 1 COMPLETE RESPONSE**

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

Dear Ms. Abelardo:

We acknowledge receipt on April 15, 2011, of your April 15, 2011, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Potiga (ezogabine) Tablets (50mg, 200mg, 300mg, 400 mg).

We consider this a complete, class 1 response to our November 30, 2010 action letter. Therefore, the user fee goal date is June 15, 2011.

If you have any questions, call Karen Abraham-Burrell, Pharm.D. Regulatory Project Manager, at (301) 796-2721.

Sincerely,

*{See appended electronic signature page}*

Karen Abraham-Burrell, Pharm.D.  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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KAREN D ABRAHAM-BURRELL  
04/26/2011

**From:** [Abelardo, Charity](#)  
**To:** [Keefe, Stephanie](#);  
**cc:** [Hall, Susan](#);  
**Subject:** Re: FDA Request for Information - NDA 022345/Potiga (ezogabine) tablets  
**Date:** Thursday, November 04, 2010 12:33:25 PM

---

Hi Stephanie,

I confirm receipt of both requests.

Kind regards,  
Charity

---

**From:** Keefe, Stephanie  
**To:** Abelardo, Charity; Hall, Susan  
**Sent:** Thu Nov 04 11:28:57 2010  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (ezogabine) tablets

Dear Dr. Hall,

Below, in [blue](#), is an additional information request. Please confirm receipt of both. Thank you,

Stephanie

---

**From:** Keefe, Stephanie  
**Sent:** Wednesday, November 03, 2010 11:30 PM  
**To:** 'Abelardo, Charity'; 'Hall, Susan'  
**Subject:** FDA Request for Information - NDA 022345/Potiga (ezogabine) tablets

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the Clinical reviewer:

**In reference to case; patient 02 from study 3065A1-216-US, site ID 001. Information request relevant to adverse event Aplastic anemia, marrow depression on 10- May01.**

**Your response to the request of July 8, 2010 is acknowledged. Uncertainty remains on the relation between the study drug and the persistent pancytopenia. The case report indicates pancytopenia occurred in 1999. Please provide the hemograms (CBC with diff) from this episode of pancytopenia if available. Please provide the hemograms for the interval from hospital discharge to study withdrawal. Please provide narrative follow up on patient health status at the time of the October 1, 2001 hemogram results. Did the patient have any signs and symptoms related to hematopoietic dysfunction at that time (October 2001) or thereafter?**

**In reference to case; patient 02 from study 3065A1-216-US, site ID 001. Information request relevant to adverse event Aplastic anemia, marrow depression on (b) (6). Addendum to request of November 3, 2010**

**In order to determine if the persistent pancytopenia is confounded by an alternate medication please provide concomitant medications which are relevant to marrow suppression for the interval from May 20, 2001 to October 1, 2001.**

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: stephanie.keefe@fda.hhs.gov

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/s/  
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STEPHANIE N KEEFE  
11/04/2010

**Keefe, Stephanie**

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**From:** Abelardo, Charity [Charity.Abelardo@Valeant.Com]  
**Sent:** Thursday, October 14, 2010 9:26 PM  
**To:** Keefe, Stephanie  
**Cc:** Hall, Susan  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (ezogabine) tablets

Hi Stephanie,

Thank you for the email below. I will let you know if we are not able to respond within the timeframe requested.

Kind regards,  
Charity

**Charity Abelardo, RAC**  
Regulatory Affairs  
**Valeant Pharmaceuticals North America**

☎: +1 (949) 461 6004 Mobile: +1 (949) 310 8422  
✉: [charity.abelardo@valeant.com](mailto:charity.abelardo@valeant.com)

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Thursday, October 14, 2010 6:18 PM  
**To:** Hall, Susan; Abelardo, Charity  
**Subject:** FDA Request for Information - NDA 022345/Potiga (ezogabine) tablets

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the Clinical reviewer:

**The sponsor is asked to provide values for the preferred terms in table 188 of the ISS which clearly occurred after the discontinuation of ezogabine treatment. A clarification of the values of table 187 for taper of > 7 days is also requested.**

Table 188 of the ISS section 5.7.2 (adverse events and SAEs upon abrupt discontinuation of study drug) is considered a basis for assessing ezogabine withdrawal effects because of the implication that the events listed in the table were precipitated due to the cessation of ezogabine treatment. This table is therefore the basis of section 9.3 (Dependence) in labeling.

The entries for two adverse event terms in table 188 were tested using the adverse event dataset. The preferred terms chosen were “psychotic disorder” and “hallucination, visual”. Two fields from the AE dataset were used to capture patients whose adverse event terms were related to abrupt discontinuation, the first was the ABDIS field. The second was a created field, which compared the adverse event start date to the last ezogabine dose date. In this field, those patients whose AESTDT1 was greater than

LDOSED T were captured. All available case report narratives were reviewed to determine the relationship of the adverse event to ezogabine discontinuation. The results of this analysis were found to be divergent from the entries posted in table 188. This observation causes concern that the values entered for each preferred term of table 188 do not all represent adverse events which occurred on the timeline following ezogabine discontinuation. The sponsor is asked to provide values for the preferred terms in table 188 which clearly occurred after the discontinuation of ezogabine treatment. This information is needed to determine if the adverse event was caused by ezogabine cessation or the adverse event resulted in the discontinuation of ezogabine.

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

-----  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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/s/

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STEPHANIE N KEEFE  
10/14/2010

**From:** [Keefe, Stephanie](#)  
**To:** ["Hall, Susan"; "Abelardo, Charity";](#)  
**Subject:** FDA Request for Information - NDA 022345/Potiga (ezogabine) tablets  
**Date:** Thursday, September 30, 2010 4:02:15 PM

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Dear Dr. Hall,

Below is our recommendations from the Division of Medication Error Prevention and Analysis (DMEPA) related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this recommendation in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

#### **A. Container Labels: All Strengths**

1. We acknowledge that you have differentiated the physical appearance of the tablets by using color, tablet shape, and tablet size. However, the use of the (b) (4) color for the presentation of the strength and the similar colored background waves behind the tablets (b) (4) minimizes the effectiveness of this differentiation. We recommend revising the strength by presenting each of the five strengths in a separate font color, distinct from the color used to present the proprietary name, to improve differentiation between the strengths. For example, present the 200 mg strength in yellow font, the 300 mg strength in green font, and the 400 mg strength in blue font. Select two separate and distinct font colors for the 50 mg and (b) (4) strengths.

2. Delete the color background presented behind the tablet pictures for the 50 mg and (b) (4) strengths. Leave the 200 mg, 300 mg, and 400 mg color backgrounds as they are currently presented in yellow, green, and blue, respectively.

#### **B. Titration Pack (Outside Panel)**

1. Increase the prominence of the information contained in the boxes titled "Kit Contains" and "Dosing Instructions".

(b) (4)

3. In the box titled “Dosing Instructions”, add the statement “for seven days” at the end of the instructions for week 1 and week 2.

4. On the front of the blister cards for week 1 and week 2, if space allows, present the tablet strength next to or beneath each tablet, leaving the tablet pictures as currently presented. If space does not allow, delete the tablet pictures and present the tablet strength next to or beneath each tablet.

5. On the front of the blister cards for week 1 and week 2, add vertical black lines to differentiate the days of the week.

**C. Titration Pack (Inside Panel)**

Revise the week 1 instructions corresponding to the time of day to read “(b) (4)”. As currently presented, it reads (b) (4).

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: stephanie.keefe@fda.hhs.gov

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/s/

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STEPHANIE N KEEFE

09/30/2010



NDA 022345

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

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 October 30, 2009 New Drug Application (NDA) 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.

On August 26, 2010, we received your August 26, 2010, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 30, 2010.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 30, 2010.

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

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Division Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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RUSSELL G KATZ  
08/30/2010



NDA 22-345

**INFORMATION REQUEST**

Valeant Pharmaceuticals North America  
Attention: Susan T. Hall, Ph.D.  
Head of Neurology R&D and Regulatory Compliance  
One Enterprise  
Aliso Viejo, CA 92656

Dear Dr. Hall:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Potiga (retigabine) 50 mg, (b) (4) 200 mg, 300 mg, and 400 mg tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1.



2. Based on the provided data, the following dissolution method and specification are recommended.

Apparatus: USP apparatus II (paddle)  
Media: 0.1N HCl at 37°C  
Volume: 1000 mL  
Rotation: 50 rpm  
Specification: Q = (b) (4) at 30 min

If you have any questions, call Teshara Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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ORIG-1

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VALEANT  
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LS NORTH  
AMERICA

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RETIGABINE

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/s/  
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RAMESH K SOOD  
08/16/2010



NDA 022345

**Pre-Approval REMS Notification**

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) submitted October 30, 2009, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Potiga (ezogabine) 50 mg, <sup>(b) (4)</sup> 200 mg, 300 mg, and 400 mg Tablets.

**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)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Potiga (ezogabine) to ensure that the benefits of the drug outweigh the increased risk of suicidal thoughts and behavior associated with the class of antiepileptic drugs (AEDs), of which Potiga (ezogabine) is a member, and the increased risk of urinary retention and its associated morbidities.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Potiga (ezogabine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Potiga (ezogabine). FDA has determined that Potiga (ezogabine) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Potiga (ezogabine). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Potiga (ezogabine).

**Communication Plan:** We have determined that a communication plan targeted to healthcare providers (e.g., neurologists, neurosurgeons, urologists, emergency room physicians and pharmacists) who are likely to prescribe or be consulted on patients using Potiga (ezogabine) will support implementation of the elements of your REMS for a period of 7 years. The communication plan must provide for the dissemination of information about the increased risk of urinary retention and its associated morbidities. The communication plan should also include information on the appropriate ways in which to monitor for and mitigate that risk.

The communication plan must include, at minimum, letters to health care providers and web-based informational sites.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. You should specify the reporting interval that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Potiga (ezogabine). Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents and the Medication Guide as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Before we can continue our evaluation of NDA 022345, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the

Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022345  
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022345  
PROPOSED REMS-AMENDMENT**

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

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

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Division Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center of Drug Evaluation and Research

Enclosure: Appendices A and B

**APPENDIX A: REMS TEMPLATE**

*If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.*

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL:**

List the goals and objectives of the REMS.

**II. REMS ELEMENTS:**

**A. Medication Guide**

*If a Medication Guide is included in the proposed REMS, include the following:*

A Medication Guide will be dispensed with each [drug name] prescription.

**B. Communication Plan**

*If a Communication Plan is included in the proposed REMS, include the following:*

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

**C. Elements To Assure Safe Use**

*If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:*

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

#### **D. Implementation System**

*If an Implementation System is included in the proposed REMS, include the following:*

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

#### **E. Timetable for Submission of Assessments**

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

**APPENDIX B:**  
**REMS SUPPORTING DOCUMENT**

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Additional Potential Elements
    - i. Medication Guide - Describe in detail how you will comply with 21 CFR 208.24.
    - ii. Patient Package Insert
    - iii. Communication Plan
  - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
  - c. Implementation System
  - d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under an NDA or BLA)
6. Other Relevant Information

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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ERIC P BASTINGS  
08/16/2010  
Signed for Dr. Katz



NDA 022345

**INFORMATION REQUEST**

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) submitted on October 30, 2009, received on October 30, 2009 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Potiga (ezogabine) 50 mg, (b) (4) 200 mg, 300 mg, and 400 mg tablets.

After a review of the materials submitted in the NDA, we conclude that ezogabine has abuse potential and recommend placement in Schedule (b) (4) of the Controlled Substances Act.

We recommend that you report to FDA all cases of abuse, misuse, overdose and addiction associated with ezogabine after its introduction on the market.

We request that you provide draft text for the label for Sections 9.2 and 9.3 of the Drug Abuse and Dependence section (Section 9.0), with language that captures the safety risks associated with high doses of ezogabine in the context of abuse (b) (4). Please submit this language within 7-10 days.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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RUSSELL G KATZ  
07/13/2010

**From:** [Keefe, Stephanie](#)  
**To:** ["Hall, Susan"; "Abelardo, Charity";](#)  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Thursday, July 08, 2010 3:28:12 PM

---

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the Clinical reviewer:

[Additional information on case patient 02 from study 3065A1-216-US, site ID 001](#)

[information request relevant to adverse event Aplastic anemia, marrow depression on \[REDACTED\] \(b\) \(6\).](#)

[1. Baseline CBC data](#)

[2. laboratory results from all studies performed during hospitalization \[REDACTED\] \(b\) \(6\) \[REDACTED\] studies noted on page 39 and 40 of patient case report form. Mission critical results are:](#)

- [a. full CBC results](#)
- [b. bone marrow biopsy results](#)
- [c. vitamin B12, folate, ferritin](#)
- [d. EBV serology](#)
- [e. HIV antibody](#)
- [f. hepatitis serology](#)
- [g. ALT, AST, GGT, total bilirubin results](#)
- [h. PPD](#)

[3. Follow up CBC results beyond 7/30/01 if available](#)

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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ORIG-1

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VALEANT  
PHARMACEUTICA  
LS NORTH  
AMERICA

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RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
07/08/2010

From: [Abelardo, Charity](#)  
To: [Keefe, Stephanie](#); [Hall, Susan](#);  
Subject: Re: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
Date: Friday, June 25, 2010 3:41:59 PM

---

Hi Stephanie,

Thank you for your email. I will get back to you as soon as possible if we are unable to respond within the time frame requested.

Kind regards,  
Charity

---

From: Keefe, Stephanie  
To: Hall, Susan; Abelardo, Charity  
Sent: Fri Jun 25 15:06:23 2010  
Subject: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the below 2 comments from our Clinical reviewer:

**1.) Please provide the following for this patient: 3065 A1-205~000032~000448**

**For hospitalization (b) (6) and follow up laboratory values-**

- 1. blood culture results**
- 2. daily temperature record**
- 3. urine culture results**
- 4. daily CBC and chemistries**

**4. hospital course - was ICU stay necessary, was there hemodynamic instability, was pressor support needed. (hospital discharge summary would be most useful)**

**5. full diagnosis, did treating physicians feel there was urosepsis, pyelonephritis**

**6. determine if evaluation for hepatobiliary obstruction was performed**

**7. follow up laboratory values- post hospitalization**

**The purpose of this information request is to fully understand the nature of the illness that began on day 19. Currently there is a deficit in the available data, primarily the hospitalization, which prevents a full analysis of the cause of the ALT and bilirubin elevation ( which reached a level of 3.8 ULN, not noted in the case report)**

**2.) We have noted in you discussion of sensitivity analysis of study 205 that location / access to investigator records for 5 sites was pending. Has resolution to this issue been submitted? Please direct the reviewer to the resolution of this issue if available. I have copied the relevant section of the ISE below for ready reference in paragraph 2.**

#### **1.7.6. Sensitivity Analyses Excluding Data from Selected Study Sites in Study 205**

Study 205 was conducted by Wyeth and completed in 2001. As noted in Section 1.2.1, the development of retigabine has involved several changes in corporate sponsors. When Valeant acquired the rights to retigabine in 2005 from Xcel Pharmaceuticals, it obtained the Wyeth study records (including case report forms [CRFs] and electronic datasets) for the trial. In preparation for the marketing applications, contact with all of the Study 205 investigators was pursued to notify them of the planned NDA/MAA submissions. In addition, site visits were initiated at selected study centers in order to confirm current contact information and verify appropriate record keeping and access to the study files.

During the course of document review at one site (site #021), multiple GCP compliance issues were identified (e.g., informed consent procedure/documentation issues; see summary of findings located in [m5.3.5.1](#)). A sensitivity analysis that excludes efficacy data from this site has been conducted. All safety data in relation to this site are reported in the ISS ([m5.3.5.3](#)) and [m2.7.4](#).

**As a separate issue, the location/access to the investigator records has yet to be confirmed at an additional 5 (site #022, #052, #054, #070, #081) out of the 73 sites that participated**

**in Study 205.** Although efforts remain ongoing to obtain documentation, a sensitivity analysis has been conducted that excludes the efficacy data from these 5 sites in addition to the single site (site #021) where significant GCP compliance issues were identified.

All safety data in relation to these sites are reported in the ISS ([m5.3.5.3](#)) and [m2.7.4](#).

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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STEPHANIE N KEEFE  
06/28/2010



NDA 22-345

**INFORMATION REQUEST**

Valeant Pharmaceuticals North America  
Attention: Sue Hall, Senior VP, Head of Neurology R&D & RA Compliance  
One Enterprise  
Aliso Viejo, CA 92656

Dear Ms. Hall:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Potiga (ezogabine) Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding validation of the HPLC Method 1 for drug-related impurities in retigabine, provide data to demonstrate retigabine assay linearity ranging from the limit of quantitation (LOQ) to 120% of nominal concentration to cover the quantitation of individual unspecified impurities.

2.



3. Provide data regarding the dissolution profile comparisons between the lower strengths (50, (b) (4), 200 and 300 mg) and the highest strength (400 mg) at higher pH's (b) (4) performed in the media without any surfactant.
4. Provide an explanation for the observed dissolution profile differences between the lower strengths (50 mg and (b) (4) and 400 mg strength at pH 1.2.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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RETIGABINE

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/s/  
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RAMESH K SOOD  
06/25/2010

From: [Keefe, Stephanie](#)  
To: ["Hall, Susan"](#);  
cc: ["Abelardo, Charity"](#);  
Subject: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
Date: Tuesday, June 22, 2010 1:40:22 PM

---

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the below comment from our Clinical reviewer:

***Can you contact the sponsor for NDA 22345 (Potiga) and ask if there is any body temperature data available from the hospitalization of [REDACTED] (b) (6) on subject: 3065 A1-205~000032~000448.***

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov).

| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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/s/

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STEPHANIE N KEEFE  
06/22/2010

**From:** [Keefe, Stephanie](#)  
**To:** ["Abelardo, Charity"](#)  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Monday, June 07, 2010 11:50:56 AM

---

[Charity,](#)

The information provided in this email is adequate. Thank you.

[Stephanie](#)

---

**From:** Abelardo, Charity [mailto:Charity.Abelardo@Valeant.Com]  
**Sent:** Friday, June 04, 2010 1:35 PM  
**To:** Keefe, Stephanie  
**Cc:** Hall, Susan  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

[Hi Stephanie,](#)

As this was a study in juvenile mice, the study was discussed in the Juvenile Toxicity Section (m2.6.6.6.4) and the Report was provided in the corresponding Nonclinical Reports Section (m4.2.3.5.4) of the original application (Sequence 0000).

Please confirm if this clarification requires a formal submission to be made or if the information provided in this email is adequate.

Please let me know if you have any additional questions.

Kind regards,  
[Charity](#)

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America  
Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Thursday, June 03, 2010 7:59 PM  
**To:** Abelardo, Charity

Cc: Hall, Susan

**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Below is a request from the Non-Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

**\* Please see the comment below from the Non-Clinical reviewer:**

***Could you ask the sponsor to provide the following or show us where it is located in the NDA:***

***A preliminary dose-finding study for the neonatal mouse carcinogenicity study ( [REDACTED] <sup>(b) (4)</sup> Study No. 05-2897; Sponsor Study No. PR2005-040)***

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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STEPHANIE N KEEFE  
06/22/2010



NDA 22-345

**INFORMATION REQUEST**

Valeant Pharmaceuticals North America  
Attention: Susan T. Hall, Ph.D.  
Head of Neurology R&D and Regulatory Compliance  
One Enterprise  
Aliso Viejo, CA 92656

Dear Dr. Hall:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Potiga (retigabine) 50 mg, (b) (4) 200 mg, 300 mg, and 400 mg tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding the (b) (4) impurity i.e., (b) (4) (b) (4) provide data to support your rationale for not monitoring its levels in the drug substance synthesis-related intermediates or in the drug substance batches.
2. Regarding the drug substance commercial manufacturing process:
  - a) Provide a list of the intermediate specifications
  - b) Describe the in-process tests for each step with acceptance criteria
  - c) Describe the critical process parameters at each step in a tabulated form and explain how the ranges for these parameters were determined.
3. Regarding (b) (4) impurity, its designation as a genotoxic or non-genotoxic impurity is under Pharmacology /Toxicology review. However, since the levels of (b) (4) in all the commercial batches of retigabine are in the range of (b) (4), an acceptance limit of NMT (b) (4) is not acceptable. Revise the proposed acceptance limit for (b) (4) in the drug substance to reflect the observed data concerning its levels in the commercial batches.
4. Regarding the impurity, (b) (4), a known mutagen, and Ames-positive impurity, (b) (4), you have proposed that routine testing for these two impurities be discontinued if the data from 15 commercial batches of retigabine drug substance reveal that the acceptance limits for these impurities are routinely met. Given the fact that (b) (4) and (b) (4) are genotoxic impurities, and

their combined levels in the four commercial batches of retigabine barely meet the specification limit of NMT (b) (4) (i.e., approximately (b) (4) based on the highest proposed daily dose of 1200 mg retigabine/day), your (b) (4), proposal is not acceptable. We ask that routine monitoring for these impurities be continued as a release test for all the commercial batches of the drug substance.

5. You have proposed that if the (b) (4) levels in 15 commercial batches are found to be within the specification limit i.e., (b) (4) routine (b) (4) testing of the drug substance will be discontinued. This (b) (4), proposal, in the current submission, is not acceptable. This issue can be addressed through a post-approval supplement once you have gathered sufficient batch analysis data and experience using the commercial manufacturing process.
6.  (b) (4)
7. Provide particle size distribution data on drug substance stability studies to rule out agglomeration on storage.
8. Regarding continued monitoring of drug substance stability, post-approval commitment is inadequate. Amend the post-approval commitment to include testing the stability batches of retigabine, prepared by proposed commercial process involving (b) (4), and to submit the data to the Agency periodically.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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RAMESH K SOOD  
05/28/2010



NDA 22-345

**INFORMATION REQUEST**

Valeant Pharmaceuticals North America  
Attention: Susan T. Hall, Ph.D.  
Head of Neurology R&D and Regulatory Compliance  
One Enterprise  
Aliso Viejo, CA 92656  
Dear Dr. Hall:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Potiga (retigabine) 50 mg, (b) (4) 200 mg, 300 mg, and 400 mg tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The proposed dissolution method using a (b) (4) paddle rotation speed and the proposed dissolution specification are less than optimal. To support and justify the selection of the (b) (4) paddle speed, provide dissolution profile data for both, 50 rpm and (b) (4) paddle rotation speeds using the proposed testing conditions [i.e., Apparatus II (paddle), 1000 ml 0.1N HCl at 37°C]. A recommendation for the dissolution acceptance criterion will be given after these data are reviewed.
2. To compare the performance of the drug product manufactured using the (b) (4) drug substance vs. the drug product manufactured using the (b) (4) drug substance; provide comparative dissolution profile data (using 50 rpm paddle rotation speed) in three dissolution media ((b) (4) and similarity f2 values.
2. You may request that FDA waives the CFR requirement for the submission of in vivo BA/BE data for lower 50, (b) (4) 200, and 300 mg strengths of your product. The waiver request should be supported by the following information; **1)** Acceptable bioequivalence data for the highest 400 mg strength, **2)** data showing that the formulation for all the strengths are (b) (4), and **3)** dissolution profile and f2 data in three dissolution media using 50 rpm paddle rotation speed.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application  
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RAMESH K SOOD  
05/03/2010

From: [Keefe, Stephanie](#)  
To: ["Abelardo, Charity":](#)  
cc: ["Hall, Susan"; Ware, Jacqueline H;](#)  
Subject: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
Date: Monday, April 12, 2010 10:49:09 AM

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Dear Dr. Hall,

Below is a request from the Urological team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the questions below from the Urological reviewer:

***1) In your January 26, 2010, response to our January 19, 2010 eMAIL request for information, you stated that a chemical analysis was performed of urine samples containing crystals, and that mass spectroscopy demonstrated peaks corresponding to the known molecular weight of retigabine and its dimer. You further state the exact nature of the crystals was not fully elucidated. Was a chemical analysis (mass spectroscopy) conducted of the amorphous urine crystals themselves? If so, what did mass spectroscopy of the amorphous crystals show? If not, why was such an analysis not carried out?***

***2) In Study 205, Patient #0125 was reported to experience renal colic due to urolithiasis. This 39 year old male started study medication on November 24, 1999 and the adverse event was reported on [REDACTED] (b) (6). The patient was reported to have an obstructing left distal ureteral calculus with left hydronephrosis. He was surgically treated with stone fragmentation. The stone was chemically analyzed and identified as calcium oxalate monohydrate. Was the stone chemically examined (e.g., using mass spectroscopy) for presence of retigabine or its dimer? If so, what was the result? If not, is the stone still available for examination by mass spectroscopy for presence of retigabine or its dimer?***

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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ORIG-1

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STEPHANIE N KEEFE  
06/22/2010

From: [Keefe, Stephanie](#)  
To: ["Abelardo, Charity"](#):  
Subject: RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
Date: Wednesday, April 07, 2010 6:05:25 PM

---

[Charity,](#)

Please find the Clinical Pharmacology reviewers comments embedded below:

(1) Please provide a Definition file associated with the electronic data sets for individual concentration-time data and PK data in SAS Transport files (.XPT). Otherwise, please direct us to where that file is if it has been submitted. This information is in the dataset folder located in Module 5 of the 120 day update (Sequence 0007; February 26, 2010). The file path is: [\m5\datasets\rtg113287\analysis](#). The definition file and all the datasets for the study are located here.

***The Definition file has been located so resubmission is not necessary.***

(3) Provide a tabulated summary of the reference and test drug formulations used in this study, such as batches, lot, expiry, etc. The certificates of analysis are included as part of the complete study report located in Module 5.3.1.2 of the 120 day update provided in Sequence 0007 on February 26, 2010 ([m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\rtg113287](#)). However, we will provide a tabulated summary including all of the requested information for ease of review.

***We were aware of the Certificates of Analysis but question the adequacy of the information necessary for the study and review. We will await for a more comprehensive summary.***

[Stephanie N. Keefe](#)

---

From: Abelardo, Charity [mailto:[Charity.Abelardo@Valeant.Com](mailto:Charity.Abelardo@Valeant.Com)]  
Sent: Wednesday, April 07, 2010 4:32 PM  
To: Keefe, Stephanie  
Subject: RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

[Hi Stephanie,](#)

Please see response below to Item (1) and (3) from the Clinical Pharmacology reviewer's request:

(1) Please provide a Definition file associated with the electronic data sets for individual concentration-time data and PK data in SAS Transport files (.XPT). Otherwise, please direct us to where that file is if it has been submitted. This information is in the dataset folder located in Module 5 of the 120 day update (Sequence 0007; February 26, 2010). The file path is: \m5\datasets\rtg113287\analysis. The definition file and all the datasets for the study are located here.

(3) Provide a tabulated summary of the reference and test drug formulations used in this study, such as batches, lot, expiry, etc. The certificates of analysis are included as part of the complete study report located in Module 5.3.1.2 of the 120 day update provided in Sequence 0007 on February 26, 2010 (m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\rtg113287). However, we will provide a tabulated summary including all of the requested information for ease of review.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America  
Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Wednesday, April 07, 2010 11:27 AM  
**To:** Abelardo, Charity  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Charity,

In response to your email, the Clinical Pharmacology reviewer has forwarded the following response:

Please respond to the information request, as listed below, to the Agency, at an earliest possible time:

(1) Please provide a Definition file associated with the electronic data sets for individual concentration-time data and PK data in SAS Transport files (.XPT). Otherwise, please direct us to where that file is if it has been submitted

(2) Bioanalytical Report for within-study bioanalytical performance/QC for Study RTG113287, as well as details for the bioanalytical site

(3) Provide a tabulated summary of the reference and test drug formulations used in this study, such as batches, lot, expiry, etc.

Please let me know if you have additional question/concerns. Thank you,

Stephanie N. Keefe

---

**From:** Abelardo, Charity [mailto:Charity.Abelardo@Valeant.Com]  
**Sent:** Wednesday, April 07, 2010 11:31 AM  
**To:** Keefe, Stephanie  
**Cc:** Hall, Susan  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Hi Stephanie,

We are in the process of preparing a response to the request from the Clinical Pharmacology reviewer provided below, but I thought that it would be useful to direct the reviewer to the complete report provided in the 120 day safety update (Sequence 0007) dated February 26, 2010. Can you confirm that the reviewer has been able to successfully access the full report provided in this submission.

Mank thanks in advance.  
Kind regards,

Charity

Charity A. Abelardo, RAC  
Regulatory Affairs Consultant  
Valeant Pharmaceuticals North America  
Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Tuesday, April 06, 2010 8:34 AM  
**To:** Hall, Susan  
**Cc:** Abelardo, Charity  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Importance:** High

Dear Dr. Hall,

Below is a request from the Clinical Pharmacology team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the Clinical Pharmacology reviewer:

The sponsor should provide the Agency a comprehensive final study report for the review. Please submit the missing information from the study report that are necessary for the review at an earliest possible time.

- (1) Electronic data sets for individual concentration-time data and PK data in SAS Transport files (.XPT)
- (2) Bioanalytical Report for within-study bioanalytical performance/QC for Study RTG113287, as well as details for the bioanalytical site
- (3) Information regarding drug formulations used in this study, such as batches, lot, expiry, etc
- (4) Explanation on why we should use the BE data you provided in Study RTG113287 and justification regarding the sample size determination for providing adequate power for BE demonstration.

Please respond to this request within 3-5 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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STEPHANIE N KEEFE  
06/22/2010

**From:** [Abelardo, Charity](#)  
**To:** [Keefe, Stephanie](#);  
**cc:** [Hall, Susan](#);  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Wednesday, March 31, 2010 10:22:16 AM  
**Attachments:** [Pages from iss-lab-value conversion.pdf](#)  
[ole0.bmp](#)

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Hi Stephanie,

GI/L is an SI unit of measure. There is a Laboratory Value Conversion table included as an appendix to the ISS (Appendix 7.11, page 611-612[attached]) which indicates GI/L is  $10^9/L$ .

I trust this reference will be helpful to the reviewer. Please let me know if you have any additional questions or require additional clarification.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America

Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Tuesday, March 30, 2010 11:28 AM  
**To:** Abelardo, Charity  
**Cc:** Hall, Susan  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the below comment from our Clinical reviewer:

***Can you write the sponsor and ask them what unit of measure this is for hematologic parameters, and what does it stand for, I cannot find in anywhere.***

***GI/L, used in the line listings for PCC values:***

**Picture (Enhanced Metafile)**

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22345

-----  
ORIG-1

-----  
VALEANT  
PHARMACEUTICA  
LS NORTH  
AMERICA

-----  
RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
03/31/2010

From: [Keefe, Stephanie](#)  
To: ["Abelardo, Charity":](#)  
cc: ["Hall, Susan":](#)  
Subject: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
Date: Tuesday, March 30, 2010 4:34:57 PM

---

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the below comment from our Clinical reviewer:](#)

***We have a request for additional information, report of bilirubin laboratory values from case 50711, study VRX-RET-E22-304. This subject had a serious elevation of ALT and AST in May of 2008 but no bilirubin values are presented. Review of the case report form also reveals no bilirubin results. Bilirubin studies concurrent with the elevated transaminase values are essential to fully characterize this hepatic adverse event.***

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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STEPHANIE N KEEFE  
06/22/2010

**From:** [Keefe, Stephanie](#)  
**To:** ["Abelardo, Charity":](#)  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Wednesday, February 24, 2010 10:41:54 AM

---

[Charity,](#)

[The CSS reviewer has an additional request. Please see their comment below:](#)

The reviewer in the Controlled Substance Staff who has been assigned to review the NDA for retigabine (Potiga; NDA 22-345) is having trouble with the links in the "Evaluation of Drug Abuse Liability" section of the NDA. Whenever she clicks on a link for a study, which should bring her to the original study itself so she can review the protocol and the data, she instead gets routed to someplace in the reference section of the document, with no further links available.

Could you please ask the Sponsor to address this apparent malfunction?

[Thank you,](#)

[Stephanie N. Keefe](#)

---

**From:** Abelardo, Charity [mailto:[Charity.Abelardo@Valeant.Com](mailto:Charity.Abelardo@Valeant.Com)]  
**Sent:** Thursday, February 18, 2010 4:52 PM  
**To:** Keefe, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

[Hi Stephanie,](#)

[I think we have what we need now. No need for a telecon on Monday, but thank you very much for your quick response and communication with the reviewer to make it happen if needed.](#)

[Kind regards,](#)  
[Charity](#)

[Charity A. Abelardo, RAC](#)  
[Regulatory Affairs](#)  
[Valeant Pharmaceuticals](#)  
[Direct - 949 461 6004](#)  
[Mobile - 949 310 8422](#)

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Thursday, February 18, 2010 9:51 AM  
**To:** Abelardo, Charity  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Charity,

The CSS reviewer provided the following comment and stated they would have a TCON on Monday to discuss any additional questions. Please advise as to whether this is appropriate:

There is a dataset named "TSMSEEP.xpt". If the sponsor can locate this dataset, they should see a lot of datasets for this particular study.

Most information that I requested should be in tsmseep.xpt. However, I found records only for 7 subjects below:

VRX-RET-E22-108~000001~009001

VRX-RET-E22-108~000001~009002

VRX-RET-E22-108~000001~009008

VRX-RET-E22-108~000001~009014

VRX-RET-E22-108~000001~009020

VRX-RET-E22-108~000001~009024

VRX-RET-E22-108~000001~009029

The sponsor should include all patients who attended treatment phase. Based on their report, a total of 36

subjects were randomized to the Treatment Phase and received at least one dose of study drug. Twenty-six

subjects completed the study, had no major protocol violations, and were included in the pharmacodynamic analysis.

Stephanie N. Keefe

---

**From:** Abelardo, Charity [mailto:Charity.Abelardo@Valeant.Com]  
**Sent:** Thursday, February 18, 2010 12:12 PM  
**To:** Keefe, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Hi Stephanie,

As mentioned in my voicemail message, the reference to Section 5.3.5.4.25.3 is not clear to us. Perhaps it would be helpful if we could contact the reviewer directly to ensure we fully understand what is being requested. Please let me know if this would be acceptable.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals

Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Wednesday, February 17, 2010 8:39 AM  
**To:** Abelardo, Charity  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Charity,

Please see the following response from our CSS reviewer:

The dataset requested is from study VRX-RET-E22-108, A Randomized Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Retigabine in Recreational Polydrug Users. This dataset may be generated from those datasets in Section 5.3.5.4.25.3.

Please let me know if you have any further questions or concerns. Thank you.

Stephanie N. Keefe

---

**From:** Abelardo, Charity [mailto:Charity.Abelardo@Valeant.Com]  
**Sent:** Tuesday, February 16, 2010 5:41 PM  
**To:** Keefe, Stephanie  
**Cc:** Hall, Susan  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Hi Stephanie,

Can you clarify what study the dataset is requested for? Is this request for a custom data display? We are also unclear as to which data domain is being asked for. Question and Finding is specified, so we believe this must apply to a specific data domain/CRF page?

Many thanks in advance for obtaining clarification.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America  
Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Tuesday, February 16, 2010 11:54 AM  
**To:** Abelardo, Charity  
**Cc:** Hall, Susan

**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the CSS team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the CSS reviewer:

[Would you please ask the sponsor to provide the dataset described in the attachment?](#)

<<data request.xls>>

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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STEPHANIE N KEEFE  
06/22/2010



NDA 022345

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Valeant Pharmaceuticals North America  
One Enterprise  
Aliso Viejo, California 92656

ATTENTION: Susan T. Hall, Ph.D.  
Senior Vice President, Head of Neurology R&D & Regulatory Compliance

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 Retigabine Tablets, 50 mg, (b) (4) 200, mg, 300 mg, and 400 mg.

We also refer to your November 20, 2009, correspondence, received November 20, 2009, requesting a review of your proposed proprietary name, Potiga. We have completed our review of the proposed proprietary name, Potiga, and have concluded that it is acceptable.

The proposed proprietary name, Potiga, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 20, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Stephanie Keefe at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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/s/

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DENISE P TOYER on behalf of CAROL A HOLQUIST  
02/18/2010

**From:** [Keefe, Stephanie](#)  
**To:** ["Abelardo, Charity":](#)  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Wednesday, February 17, 2010 11:39:28 AM

---

[Charity,](#)

[Please see the following response from our CSS reviewer:](#)

The dataset requested is from study VRX-RET-E22-108, A Randomized Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Retigabine in Recreational Polydrug Users. This dataset may be generated from those datasets in Section 5.3.5.4.25.3.

[Please let me know if you have any further questions or concerns. Thank you.](#)

[Stephanie N. Keefe](#)

---

**From:** Abelardo, Charity [mailto:[Charity.Abelardo@Valeant.Com](mailto:Charity.Abelardo@Valeant.Com)]  
**Sent:** Tuesday, February 16, 2010 5:41 PM  
**To:** Keefe, Stephanie  
**Cc:** Hall, Susan  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

[Hi Stephanie,](#)

[Can you clarify what study the dataset is requested for? Is this request for a custom data display? We are also unclear as to which data domain is being asked for. Question and Finding is specified, so we believe this must apply to a specific data domain/CRF page?](#)

[Many thanks in advance for obtaining clarification.](#)

[Kind regards,](#)  
[Charity](#)

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America  
Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Tuesday, February 16, 2010 11:54 AM  
**To:** Abelardo, Charity  
**Cc:** Hall, Susan  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the CSS team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the CSS reviewer:

[Would you please ask the sponsor to provide the dataset described in the attachment?](#)

<<data request.xls>>

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: stephanie.keefe@fda.hhs.gov

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disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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STEPHANIE N KEEFE  
06/22/2010

**From:** [Abelardo, Charity](#)  
**To:** [Keefe, Stephanie](#);  
**cc:** [Hall, Susan](#);  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Tuesday, February 16, 2010 10:00:54 AM

---

Dear Stephanie,

We are working to provide the ECG dataset of the moxifloxacin and placebo subjects at the two requested time points of 15 and 30 minutes post-dose, by March 2, 2010. Our ECG vendor was shut down due to the snow storm this past week, thus it took a week to initiate this work order due to the weather. Please communicate this timeline to the QT-IRT reviewer and advise if the ECG dataset (without the double delta QTcF calculation) to be provided by March 3, is sufficient. If a descriptive statistical analysis is also required we will need to provide this subsequent to the provision of the dataset. Further, can you confirm that the xml transfer files should be uploaded to the ECG data warehouse?

Many thanks in advance for your response.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America  
Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Monday, February 08, 2010 2:25 PM  
**To:** Abelardo, Charity  
**Cc:** Hall, Susan  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the QT-IRT team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a

formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the QT-IRT reviewer:

The moxifloxacin profile is not what we expected. The rising phase is missing. The maximum moxifloxacin induced  $\Delta\Delta\text{QTcF}$  effect reaches peak almost at the first available time point, which is 1 hr after dose. We want to understand what happened before 1 hour. Please extract data for moxifloxacin, placebo at 15 minute, 30 minute post-dose and the corresponding baseline for us to evaluate.

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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/s/

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STEPHANIE N KEEFE  
02/16/2010

From: [Keefe, Stephanie](#)  
To: ["Abelardo, Charity"](#):  
Subject: RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
Date: Sunday, February 07, 2010 9:52:05 PM

---

Charity,

In response to your request for feedback from our Statistical reviewer:

1. The ANCOVA model in your request for Studies 301 and 302 includes region as a covariate that was one of the protocol specified randomization stratification factors. There was an additional randomization stratification factor, baseline seizure frequency category ( $\leq 8$  and  $> 8$ ), for studies 301 and 302. The ICH statistical principles suggest that the statistical analyses account for the randomization stratification factors. We would like to clarify whether you would also like to include baseline seizure frequency category in the ANCOVA model.

Response: Please include REGION as a Class variable (i.e., Factor) in the ANCOVA model. Baseline frequency needs to be used as a continuous covariate in Model 1, Log (Baseline+.3) in Model 2, and Rank (Baseline) in Model 3.

2. The randomization for Study 205 was stratified by center and the efficacy analyses were adjusted for the center group. The center grouping for 205 was done by geographical region as listed below:

- 1 = Great Britain + Belgium + Netherlands
- 2 = France
- 3 = Portugal + Spain
- 4 = Croatia + Germany
- 5 = Italy
- 6 = Australia + New Zealand
- 7 = Finland + Norway + Sweden
- 8 = Poland
- 9 = Israel + Slovakia
- 10 = Czech Repub
- 11 = US

Do you want to include this center group in the ANCOVA model in the place of 'region' for Study 205? If you wish us to include 'region', can you please provide some guidance as to how you wish region to be defined as this was not pre-specified in our protocol or analysis plan.

Response: Please use CENTER GROUP as a CLASS variable in the ANCOVA models.

3. The robustness of the requested ANCOVA analysis relies on the data meeting some assumptions (e.g. normality, homogeneity of variance). Some of the requested analyses on the data of Studies 205, 301 and 302 may clearly violate the assumptions. We would like to perform some model checking analyses since the model checking analyses would be critical on the interpretation of the requested analyses. Would the reviewer wish to also review the results of the model checking analyses?

Response: Yes, the reviewer is interested in the results of the model checking analyses.

Stephanie N. Keefe

---

**From:** Abelardo, Charity [mailto:Charity.Abelardo@Valeant.Com]  
**Sent:** Friday, February 05, 2010 3:54 PM  
**To:** Keefe, Stephanie  
**Cc:** Hall, Susan  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Hi Stephanie,

I wanted to follow-up with regard to our request for feedback below. In order to complete the response to the statistical reviewers request we do need to clarify the points below. Has the statistical reviewer had an opportunity to review our questions? Please let me know if a call with the reviewer to discuss the points below would be helpful or if the reviewer is able to provide a response via email.

Many thanks in advance for your help.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America

Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Abelardo, Charity  
**Sent:** Monday, February 01, 2010 3:52 PM  
**To:** Keefe, Stephanie  
**Cc:** Hall, Susan  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Hi Stephanie,

We are in receipt of the request from the statistical reviewer dated January 28, 2010. After reviewing this request internally, we would like the opportunity to discuss the following points with the statistical reviewer:

1. The ANCOVA model in your request for Studies 301 and 302 includes region as a covariate that was one of the protocol specified randomization stratification factors. There was an additional randomization stratification factor, baseline seizure frequency category ( $\leq 8$  and  $> 8$ ), for studies 301 and 302. The ICH statistical principles suggest that the statistical analyses account for the randomization stratification factors. We would like to clarify whether you would also like to include baseline seizure frequency category in the ANCOVA model.

2. The randomization for Study 205 was stratified by center and the efficacy analyses were adjusted for the center group. The center grouping for 205 was done by geographical region as listed below:

- 1 = Great Britain + Belgium + Netherlands
- 2 = France
- 3 = Portugal + Spain
- 4 = Croatia + Germany
- 5 = Italy
- 6 = Australia + New Zealand
- 7 = Finland + Norway + Sweden
- 8 = Poland
- 9 = Israel + Slovakia
- 10 = Czech Repub
- 11 = US

Do you want to include this center group in the ANCOVA model in the place of 'region' for Study 205? If you wish us to include 'region', can you

please provide some guidance as to how you wish region to be defined as this was not pre-specified in our protocol or analysis plan.

3. The robustness of the requested ANCOVA analysis relies on the data meeting some assumptions (e.g. normality, homogeneity of variance). Some of the requested analyses on the data of Studies 205, 301 and 302 may clearly violate the assumptions. We would like to perform some model checking analyses since the model checking analyses would be critical on the interpretation of the requested analyses. Would the reviewer wish to also review the results of the model checking analyses?

We would appreciate it if you could communicate the above mentioned points to the statistical reviewer and let us know if the reviewer would be open to a brief discussion to clarify the request and our proposed approach. We would like to obtain clarification as soon as possible in order to respond within the 7-10 day timeframe requested.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals International

Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]  
**Sent:** Thursday, January 28, 2010 9:07 AM  
**To:** Abelardo, Charity  
**Cc:** Hall, Susan  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the Statistical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the Statistical reviewer:

The sponsor's responses (dated 12/4/09) to the Statistics information request are okay.

I have another statistical request to the Sponsor. The request is as follows:

Let Y= The 28-day total partial seizure frequency at post baseline period

X= The 28-day total partial seizure frequency at baseline period.

Then I am interested in fitting following ANCOVA models in studies 301, 302 & 205 (consider Treatment group and Region as Class variables in the ANCOVA models and use LSMEAN comparisons between Treatment groups):

$$Y = X + \text{Treatment group} + \text{Region}$$

$$\text{LOG}(Y+0.3) = \text{Log}(X+0.3) + \text{Treatment group} + \text{Region}$$

$$\text{Rank}(Y) = \text{Rank}(X) + \text{Treatment} + \text{Region}$$

Please provide the statistical findings in tables and the SAS codes for each of the three studies (#301, #302 & #205).

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

---

**From:** Abelardo, Charity [mailto:Charity.Abelardo@Valeant.Com]

**Sent:** Friday, December 04, 2009 8:36 PM

**To:** Abelardo, Charity; Keefe, Stephanie

**Cc:** Hall, Susan

**Subject:** Response to FDA Request for Information - NDA 022345/Potiga (retigabine) tablets: Sequence 0003

Dear Ms. Keefe:

I wanted to alert you that we have completed submission today of our response to the request from the Statistical reviewer communicated in your email of November 24, 2009, below. Attached is a copy of the cover letter and our written response for your immediate reference.

Please note the response includes additional detail and points of clarification with regard to how the SAS programs have been prepared. The response provides the SAS programs for all key efficacy tables and we believe it meets the intent of the request. We have provided the most comprehensive response possible within the 7-10 day period requested. However, we acknowledge that time has not allowed us to provide SAS programs for *every* efficacy table. In order to provide the remaining SAS programs, we will need to divert resources from our ongoing efforts on the 120-day safety update. Accordingly, it is important for us to understand whether these additional data are essential therefore we have requested the reviewer's feedback on whether the contents of this submission sufficiently address the request. If additional delivery of information is necessary, we suggest a teleconference with the statistical reviewer. I will plan to follow-up with you on Monday to discuss further the need for a teleconference.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America

Direct - 949 461 6004  
Mobile - 949 310 8422

---

**From:** Keefe, Stephanie  
**To:** Hall, Susan  
**Sent:** Tue Nov 24 11:48:16 2009  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the Statistical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

**\* Please see the comment below from the Statistical reviewer:**

Please provide SAS codes (without using any SAS macro statement) for the efficacy tables and figures you have reported in the study reports (studies# 205, 301, 302, 200/201, 202, and 214) and Summary efficacy report. Do not use Format lib in the programs. Include the Format statements (if it is necessary) in the SAS programs.

Finally, please create a table as follows:

Study# Table# (as reported in the study report) SAS data set name SAS code program name\* Any comment/Instruction

\* Assume that we will save your SAS data set in the local directory "C:\Temp." Please do not use any SAS Macro statement in the SAS programming code.

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22345

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ORIG-1

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VALEANT  
PHARMACEUTICA  
LS NORTH  
AMERICA

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RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
06/22/2010

**From:** [Abelardo, Charity](#)  
**To:** [Keefe, Stephanie](#); [Hall, Susan](#);  
**Subject:** Re: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Thursday, January 14, 2010 2:30:26 PM

---

Hi Stephanie,

We have received the request from the Clinical reviewer below and will get back to you regarding our response timeframe should we see any issues in meeting the timeline.

Kind regards,  
Charity

---

**From:** Keefe, Stephanie  
**To:** Hall, Susan; Abelardo, Charity  
**Sent:** Thu Jan 14 14:10:07 2010  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comment below from the Clinical reviewer:](#)

[Can you ask the Sponsor to provide tabulated data for urinalysis for Study 301 and 303 similar to that provided for Study 205 \(Table 12-21, pg 139\) and include urine pH data somewhere. In addition, can you ask them to submit case narratives for the four cases of nephrolithiasis in study 301 and any quantitative information on the "amorphous urinary crystals."](#)

[Can you also ask them to send the case narratives for Patient 30301, 50102, 80304, 60604, and 40119 in Study 302.](#)

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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STEPHANIE N KEEFE  
01/14/2010

|                                                                                                                                                                                                                                                                                                                                                                                      |                                    |                                                                                                                                                                                                                                                                                                                        |                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                     |                                    | <b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b><br><b>**Please send immediately following the Filing/Planning meeting**</b>                                                                                                                                                                                      |                                                                                                        |
| TO:<br><b>CDER-DDMAC-RPM</b>                                                                                                                                                                                                                                                                                                                                                         |                                    | FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Russell Katz, MD, Division of Neurology Products</b>                                                                                                                                                                                                  |                                                                                                        |
| REQUEST DATE<br>January 12, 2010                                                                                                                                                                                                                                                                                                                                                     | IND NO.                            | NDA/BLA NO.<br>22-345                                                                                                                                                                                                                                                                                                  | TYPE OF DOCUMENTS<br>(PLEASE CHECK OFF BELOW)<br>New original NME NDA                                  |
| NAME OF DRUG<br><b>Potiga (retigabine) tablets</b>                                                                                                                                                                                                                                                                                                                                   | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>1                                                                                                                                                                                                                                                                                            | DESIRED COMPLETION DATE<br>(Generally 1 week before the wrap-up meeting)<br>Wrap Up mtg: June 28, 2010 |
| NAME OF FIRM:<br><b>Valeant Pharmaceuticals North America</b>                                                                                                                                                                                                                                                                                                                        |                                    | PDUFA Date: PDUFA goal date: August 30, 2010                                                                                                                                                                                                                                                                           |                                                                                                        |
| <b>TYPE OF LABEL TO REVIEW</b>                                                                                                                                                                                                                                                                                                                                                       |                                    |                                                                                                                                                                                                                                                                                                                        |                                                                                                        |
| <b>TYPE OF LABELING:</b><br>(Check all that apply)<br><input type="checkbox"/> PACKAGE INSERT (PI)<br><input type="checkbox"/> PATIENT PACKAGE INSERT (PPI)<br><input type="checkbox"/> CARTON/CONTAINER LABELING<br><input type="checkbox"/> MEDICATION GUIDE<br><input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)                                                                 |                                    | <b>TYPE OF APPLICATION/SUBMISSION</b><br><input checked="" type="checkbox"/> ORIGINAL NDA/BLA<br><input type="checkbox"/> IND<br><input type="checkbox"/> EFFICACY SUPPLEMENT<br><input type="checkbox"/> SAFETY SUPPLEMENT<br><input type="checkbox"/> LABELING SUPPLEMENT<br><input type="checkbox"/> PLR CONVERSION |                                                                                                        |
| <b>REASON FOR LABELING CONSULT</b><br><input type="checkbox"/> INITIAL PROPOSED LABELING<br><input type="checkbox"/> LABELING REVISION                                                                                                                                                                                                                                               |                                    |                                                                                                                                                                                                                                                                                                                        |                                                                                                        |
| <b>EDR link to submission:</b><br>The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA022345\022345.ENX.                                                                                                                                                                                                                                                                |                                    |                                                                                                                                                                                                                                                                                                                        |                                                                                                        |
| Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.                                                                                                  |                                    |                                                                                                                                                                                                                                                                                                                        |                                                                                                        |
| COMMENTS/SPECIAL INSTRUCTIONS: NDA 22-345 was received on October 30, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME.<br><br>Mid-Cycle Meeting: March 29, 2010<br><br>Labeling Meetings: June 15, 2010; July 6, 8, 15, 20, 22, 26, 28; August 3, 5, 9, 12, 16, 19, 24, 26<br><br>Wrap-Up Meeting: June 28, 2010 |                                    |                                                                                                                                                                                                                                                                                                                        |                                                                                                        |
| SIGNATURE OF REQUESTER<br><b>Stephanie Keefe, Regulatory Project Manager, DNP</b><br>Food and Drug Administration<br>Phone: 301-796-4098<br>Email: stephanie.keefe@fda.hhs.gov                                                                                                                                                                                                       |                                    |                                                                                                                                                                                                                                                                                                                        |                                                                                                        |
| SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                |                                    | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> eMAIL<br><input type="checkbox"/> HAND                                                                                                                                                                                                           |                                                                                                        |

| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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/s/

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STEPHANIE N KEEFE  
01/19/2010



NDA 022345

**FILING COMMUNICATION**

Valeant Pharmaceuticals North America  
Attention: Susan T. Hall, Ph.D.  
Head of Neurology R&D and Regulatory Compliance  
One Enterprise  
Aliso Viejo, CA 92656

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 (retigabine) 50 mg, (b) (4) 200 mg, 300 mg, and 400 mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 30, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 30, 2010.

During our filing review of your application, we have identified the following potential review issues:

**Clinical**

1. A sustained urologic safety signal has been identified during the progress of the IND. The events of concern have been urinary retention, increased frequency of urinary tract infection, and unidentified crystals in the urine. In light of these events, a consult has been requested from the Division of Reproductive and Urologic Products to aid in the review of this safety matter.

## **Chemistry, Manufacturing and Controls**

1. With regard to the drug substance manufacturing process, you identify two process parameters, (b) (4) as critical to control formation of the desired form (b) (4). We ask that you provide data to support the choice of these control parameters and the proposed limits.
2. With regard to the drug substance specification, we note identification tests (i.e., IR spectroscopy and X-ray powder diffraction) are included in the specification to confirm the presence of the desired form, (b) (4). You do not, however, propose limits for other polymorphic forms, or amorphous material in the bulk drug substance. We ask that you provide justification for the absence of this control. Additionally, provide supporting data regarding the sensitivity of each method for detection of alternate polymorphic forms or amorphous materials.
3. We ask that you clarify whether drug substance manufactured by the (b) (4) process, or any batches of the resulting drug product, have been placed on stability. Submit all available stability data.
4. For the lower strengths of the market image tablets (i.e., 50 mg, (b) (4) 200 mg, and 300 mg), you will need to submit either a formal biowaiver request, with appropriate supporting data, or provide bioequivalence data for these strengths.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

## **REQUESTS FOR ADDITIONAL INFORMATION**

### **Clinical Pharmacology**

1. The list below describes study reports that are not text-recognizable, with some containing incorrect hyperlinks in the TOC. Therefore, we ask that you resubmit study reports with corrected hyperlinks to the TOC. They should also be revised to an alpha/numeric format that permit text search as well as copy/paste of text, tables, and figures. The list of such reports is as follows:
  - BA/BE studies – Reports for Studies 103, 104, 120, 123, and 110 (incorrect hyperlink from TOC)
  - Human PK studies – Reports for Studies 100, 101, 102, 107, 117, 108 (incorrect links for TOC), plasma concentration monitoring to Study 108, and Fb20799
  - Intrinsic factor – Reports for Study 105
  - Extrinsic factor – Report 030001, Studies 112 and 113

2. With regard to data and programs request for population PK and exposure-response analyses:
- Please provide all datasets and programs with outputs according to the following directions:
    - "All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt)."
  - If all datasets / programs already have been submitted with valid format, please provide an exact location.

### **Chemistry, Manufacturing and Controls**

- You have submitted comparative dissolution profiles for the highest strength tablet (400 mg) of drug product manufactured using drug substance obtained from the (b) (4) process versus the drug product manufactured using drug substance obtained from the (b) (4) (Refer to Section 3.2.P.2.1, Figure 1). Provide the dissolution conditions that were used and the individual tablet data for review. Additionally, provide comparative dissolution profile data for the other tablet strengths.
- Provide the raw data for the dissolution method development, including the individual tablet dissolution value at different time points, drug product batch numbers, drug substance batch numbers and the dissolution conditions used (media, apparatus, rotation speed, etc).
- Provide the raw data for the dissolution comparison of the formulations used in the bioequivalence study (individual tablet dissolution data).
- Provide the dissolution data from the formulation development, including the individual tablet (or capsule) dissolution data along with the manufacturing parameters used for the formulations resulting in dissolution, such as particle sizes, (b) (4), and hardness. Dissolution conditions should be specified.

### **Labeling**

1. If you have not already done so, you must submit the 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **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 acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

A pediatric plan must be submitted for all deferred studies. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/ pharmacodynamics, safety, efficacy) that will be conducted. If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the following dates: (1) protocol submission; (2) study completion; and 3) submission of study reports.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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/s/

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RUSSELL G KATZ  
01/12/2010

**From:** [Abelardo, Charity](#)  
**To:** [Keefe, Stephanie](#); [Hall, Susan](#);  
**Subject:** RE: FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Tuesday, December 22, 2009 11:28:56 AM

---

Hi Stephanie,

We have received the request below. We will get back to you if we foresee any issues in responding within the timeframe requested.

Kind regards,  
Charity

Charity A. Abelardo, RAC  
Regulatory Affairs  
Valeant Pharmaceuticals North America  
Direct - 949 461 6004  
Mobile - 949 310 8422

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**From:** Keefe, Stephanie [mailto:[Stephanie.Keefe@fda.hhs.gov](mailto:Stephanie.Keefe@fda.hhs.gov)]  
**Sent:** Tuesday, December 22, 2009 7:10 AM  
**To:** Hall, Susan; Abelardo, Charity  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets

Dear Dr. Hall,

Below is a request from the Clinical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comment below from the Clinical reviewer:

Please provide a tabular presentation of protocol violations by individual study center (not pooled centers) for each of the clinical trials 205, 301 & 302. Please also provide a definition of protocol violations.

Please respond to this request within 7-10 days; if you are unable to meet

this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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ORIG-1

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VALEANT  
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AMERICA

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/s/  
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STEPHANIE N KEEFE  
12/22/2009



NDA 022345

**NDA ADVICE LETTER  
PROPRIETARY NAME ACKNOWLEDGEMENT**

Valeant Pharmaceuticals North America  
One Enterprise  
Aliso Viejo, California 92656

ATTENTION: Susan T. Hall, Ph.D.  
Senior Vice President  
Head of Neurology R&D & Regulatory Compliance

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 Retigabine Tablets, 50 mg, (b) (4) 200, mg, 300 mg, and 400 mg.

We also acknowledge receipt of your November 20, 2009, correspondence, received November 20, 2009, requesting a review of your proposed proprietary name, Potiga. We have determined that your submission is complete and will review this proposed proprietary name accordingly.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Stephanie Keefe at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Denise P. Toyer, Pharm.D.  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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VALEANT  
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RETIGABINE

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/s/  
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DENISE P TOYER  
12/22/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): **Ling Chen, Ph.D., Mathematical Statistician, OTS/OB/DBVI, HFD-705**

FROM (Name, Office/Division, and Phone Number of Requestor): **Corinne P. Moody, Science Policy Analyst, Controlled Substance Staff, (301) 796-3152**

DATE  
12-18-09

IND NO.

NDA NO.  
22-345

TYPE OF DOCUMENT

DATE OF DOCUMENT  
10-30-09

NAME OF DRUG  
**Potiga (retigabine) Tablets**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
**03-01-10**

NAME OF FIRM: **Valeant Pharmaceuticals, North America**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW                  |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY                      |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS                  |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |  |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Please provide a statistical consult of the human abuse liability studies conducted with this NME. The entire submission may be accessed at: \\CDSESUB1\EVSPROD\NDA022345\022345.ENX. If you have any questions, please e-mail me or contact me at 6-3152.

SIGNATURE OF REQUESTOR  
**Corinne P. Moody, Science Policy Analyst**

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

---

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/s/

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CORINNE P MOODY  
12/18/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): **OND /Div Reproductive and Urologic Products**  
Attn: **Victor Browne/Jennifer Mercier/ Margie Kober**

FROM (Name, Office/Division, and Phone Number of Requestor): **Russell Katz, MD, Division of Neurology Products**

DATE  
**December 15, 2009**

IND NO.

NDA NO.  
**22-345**

TYPE OF DOCUMENT  
**urinary adverse event data**

DATE OF DOCUMENT  
**October 30, 2009**

NAME OF DRUG  
**Potiga (Retigabine) Tablets**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG  
**Partial onset-seizures**

DESIRED COMPLETION DATE  
**May 30, 2010**

NAME OF FIRM: **Valeant Pharmaceuticals North America**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input checked="" type="checkbox"/> PROGRESS REPORT      | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |  |                                      |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 22-345 was received on October 30, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has a PDUFA goal date of 8-30-10. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA022345\022345.ENX.

**Reason for Consult:**

1. urinary retention / bladder atony. Several cases of Urinary retention identified which have been associated with the investigational drug use. All fully reversible after drug discontinuation except for one with partial reversibility. The latter patient continues to self cath 2 to 3 times a day- subject VRX-RET-E22-303-03505.
2. Increase in frequency of urinary tract infection
3. urinary crystals present but not identified, may be crystals of the test agent. 36% of administered dose is unchanged renal excretion.

**Questions:**

1. From your experience can you comment on the likelihood that this agent ,a potentiator of potassium channel

- opening, may be acting directly on the detrussor muscle to produce weakness of contraction.
2. From the available safety data and postulated drug mechanism of action is urinary retention likely to always be reversible, or likely to become irreversible if exposure is sustained after initial symptoms
  3. If needed in labeling, what is the best approach to monitoring for this adverse effect, symptom profile from the AUA scale, periodic bladder ultrasound, patient symptoms alone or some combination of the aforementioned parameters
  4. based on the available data do you feel that retigabine is crystallogenic, if so is this a threat to upper or lower tract function.
  5. Is there an approach to monitoring pre-emptively for crystal formation.

The relevant adverse event data is present in the NDA22345-Section 5.3.5.3.28 the ISS, appendix 7.4, renal/urinary disorders. An additional very important document summarizing urinary retention is found in NDA22345 section 1.6 (meetings) 9April 2008 Response to request date March 21, 2008 (SN523). This latter submission is an earlier summary and analysis of cases of urinary retention.

SIGNATURE OF REQUESTOR Stephanie Keefe, Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-4098 Email: stephanie.keefe@fda.hhs.gov	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22345

-----  
ORIG-1

-----  
VALEANT  
PHARMACEUTICA  
LS NORTH  
AMERICA

-----  
RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
12/17/2009

# REQUEST FOR CONSULTATION

TO (Office/Division): OSE/DRISK  
Attention: Laurie Kelley

FROM (Name, Office/Division, and Phone Number of Requestor): Russell Katz, MD, Division of Neurology Products

DATE  
December 1, 2009

IND NO.

NDA NO.  
22-345

TYPE OF DOCUMENT  
New original NME NDA

DATE OF DOCUMENT  
October 30, 2009

NAME OF DRUG  
Potiga (retigabine) tablets

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
1

DESIRED COMPLETION DATE  
May 30, 2010  
PDUFA goal date: August 30, 2010

NAME OF FIRM: Valeant Pharmaceuticals North America

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 22-345 was received on October 30, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has a PDUFA goal date of 8-30-10. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA022345\022345.ENX. Please review and comment on the proposed labeling as well as provide recommendations regarding the Risk Management plans. The filing meeting for NDA 22-345 is scheduled for 12/15 at 8:30am (WO 22 Rm. 4270) if you or someone from your group would like to attend. Draft labeling is available in module 1 section 14 and the Risk Management Plans are available in Module 1.16. Please note that because this product is an anticonvulsant, we expect it to have, at a minimum, a MedGuide-only REMS for suicidality (like the rest of the anticonvulsant class).

SIGNATURE OF REQUESTOR  
Stephanie Keefe, Regulatory Project Manager, DNP  
Food and Drug Administration  
Phone: 301-796-4098  
Email: stephanie.keefe@fda.hhs.gov

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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ORIG-1

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VALEANT  
PHARMACEUTICA  
LS NORTH  
AMERICA

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RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
12/04/2009

**From:** [Keefe, Stephanie](#)  
**To:** ["Hall, Susan"](#);  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Tuesday, November 24, 2009 11:48:16 AM

---

Dear Dr. Hall,

Below is a request from the Statistical team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comment below from the Statistical reviewer:](#)

Please provide SAS codes (without using any SAS macro statement) for the efficacy tables and figures you have reported in the study reports (studies# 205, 301, 302, 200/201, 202, and 214) and Summary efficacy report. Do not use Format lib in the programs. Include the Format statements (if it is necessary) in the SAS programs.

Finally, please create a table as follows:

Study# Table# (as reported in the study report) SAS data set name SAS code program name\* Any comment/Instruction

\* Assume that we will save your SAS data set in the local directory "C:\Temp." Please do not use any SAS Macro statement in the SAS programming code.

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098

email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov).

| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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/s/

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STEPHANIE N KEEFE  
11/24/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): OSE/DMEPA  
Attention: Laurie Kelley

FROM (Name, Office/Division, and Phone Number of Requestor): Russell Katz, MD, Division of Neurology Products

DATE  
November 20, 2009

IND NO.

NDA NO.  
22-345

TYPE OF DOCUMENT  
New original NME NDA

DATE OF DOCUMENT  
October 30, 2009

NAME OF DRUG  
Potiga (retigabine) tablets

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
1

DESIRED COMPLETION DATE  
May 30, 2010  
PDUFA goal date: August 30, 2010

NAME OF FIRM: Valeant Pharmaceuticals North America

### REASON FOR REQUEST

#### I. GENERAL

- |                                                          |                                                  |                                                            |
|----------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |                                                            |

#### II. BIOMETRICS

- |                                                 |                                                 |
|-------------------------------------------------|-------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |                                                 |

#### III. BIOPHARMACEUTICS

- |                                                  |                                                      |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |                                                                                    |                                                                              |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |                                                                              |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 22-345 was received on October 30, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has a PDUFA goal date of 8-30-10. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA022345\022345.ENX. Please review and comment on the proposed container labeling as well as provide recommendations regarding the established name (given the confusion issues raised during IND review). The filing meeting for NDA 22-345 is scheduled for 12/15 at 8:30am (WO 22 Rm. 4270) if you or someone from your group would like to attend. Draft labeling is available in module 1 section 14.

SIGNATURE OF REQUESTOR  
Stephanie Keefe, Regulatory Project Manager, DNP  
Food and Drug Administration  
Phone: 301-796-4098

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

|                                                                                     |                                         |
|-------------------------------------------------------------------------------------|-----------------------------------------|
| Email: <a href="mailto:stephanie.keefe@fda.hhs.gov">stephanie.keefe@fda.hhs.gov</a> |                                         |
| PRINTED NAME AND SIGNATURE OF RECEIVER                                              | PRINTED NAME AND SIGNATURE OF DELIVERER |

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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ORIG-1

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VALEANT  
PHARMACEUTICA  
LS NORTH  
AMERICA

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RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
11/20/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): HFD-009/Controlled Substances Staff  
Attention: Corinne Moody/ Michael Klein

FROM (Name, Office/Division, and Phone Number of Requestor): Russell Katz, MD, Division of Neurology Products

DATE  
November 12, 2009

IND NO.

NDA NO.  
22-345

TYPE OF DOCUMENT  
New original NME NDAs

DATE OF DOCUMENT  
October 30, 2009

NAME OF DRUG  
Potiga (retigabine) tablets

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
1

DESIRED COMPLETION DATE  
May 30, 2010  
PDUFA goal date: August 30, 2010

NAME OF FIRM: Valeant Pharmaceuticals North America

### REASON FOR REQUEST

#### I. GENERAL

- |                                                          |                                                  |                                                            |
|----------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |                                                            |

#### II. BIOMETRICS

- |                                                 |                                                 |
|-------------------------------------------------|-------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |                                                 |

#### III. BIOPHARMACEUTICS

- |                                                  |                                                      |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |                                                                                    |                                                                              |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |                                                                              |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 22-345 was received on October 30, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has a PDUFA goal date of 8-30-10. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA022345\022345.ENX. Please review and comment on the acceptability of the abuse liability studies submitted in NDA 22-345. The filing meeting for NDA 22-345 is scheduled for 12/15 at 8:30am (WO 22 Rm. 4270) if you or someone from your group would like to attend. Data is available in m4.2.3.7.4.

SIGNATURE OF REQUESTOR  
Stephanie Keefe, Regulatory Project Manager, DNP  
Food and Drug Administration  
Phone: 301-796-4098

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

|                                                                                     |                                         |
|-------------------------------------------------------------------------------------|-----------------------------------------|
| Email: <a href="mailto:stephanie.keefe@fda.hhs.gov">stephanie.keefe@fda.hhs.gov</a> |                                         |
| PRINTED NAME AND SIGNATURE OF RECEIVER                                              | PRINTED NAME AND SIGNATURE OF DELIVERER |

| Application Type/Number | Submission Type/Number | Submitter Name                                  | Product Name |
|-------------------------|------------------------|-------------------------------------------------|--------------|
| NDA-22345               | ORIG-1                 | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | RETIGABINE   |

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/s/

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STEPHANIE N KEEFE  
11/13/2009

**From:** [Keefe, Stephanie](#)  
**To:** ["Hall, Susan";](#)  
**cc:** ["Abelardo, Charity";](#)  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Thursday, November 12, 2009 4:23:18 PM

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Dear Susan,

In conducting a regulatory review of your NDA 022345/Potiga (retigabine) Tablets, we have been unable to locate a new request for proprietary name review. If this information was included in the original NDA submission, we ask that you resubmit it as a separate amendment to the NDA. Please note that the proprietary name must be re-evaluated under the NDA even though it was evaluated under IND 53,950. As a reminder, our letter of May 14, 2009 to IND 53,950 advised you that "A request for proprietary name review for Potiga should be submitted once the NDA is submitted."

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov).

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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ORIG-1

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VALEANT  
PHARMACEUTICA  
LS NORTH  
AMERICA

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RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
11/12/2009

**From:** [Keefe, Stephanie](#)  
**To:** ["Hall, Susan";](#)  
**cc:** [Abelardo, Charity;](#)  
**Subject:** FDA Request for Information - NDA 022345/Potiga (retigabine) tablets  
**Date:** Thursday, November 12, 2009 4:14:15 PM  
**Attachments:** [HighlightsofClinicalPharmacology.doc](#)

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Dear Dr. Hall,

Below is a request from the OT/IRT team related to their ongoing review of the Potiga application (N 22-345). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please complete the attached Clinical Pharmacology form.](#)

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Keefe  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
Silver Spring, MD 20993-0002

phone: 301-796-4098  
email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

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## Highlights of Clinical Pharmacology

|                                           |                                                                   |                                                                                                                         |
|-------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Therapeutic dose                          | Include maximum proposed clinical dosing regimen.                 |                                                                                                                         |
| Maximum tolerated dose                    | Include if studied or NOAEL dose                                  |                                                                                                                         |
| Principal adverse events                  | Include most common adverse events; dose limiting adverse events  |                                                                                                                         |
| Maximum dose tested                       | Single Dose                                                       | Specify dose                                                                                                            |
|                                           | Multiple Dose                                                     | Specify dosing interval and duration                                                                                    |
| Exposures Achieved at Maximum Tested Dose | Single Dose                                                       | Mean (%CV) Cmax and AUC                                                                                                 |
|                                           | Multiple Dose                                                     | Mean (%CV) Cmax and AUC                                                                                                 |
| Range of linear PK                        | Specify dosing regimen                                            |                                                                                                                         |
| Accumulation at steady state              | Mean (%CV); specify dosing regimen                                |                                                                                                                         |
| Metabolites                               | Include listing of all metabolites and activity                   |                                                                                                                         |
| Absorption                                | Absolute/Relative Bioavailability                                 | Mean (%CV)                                                                                                              |
|                                           | Tmax                                                              | <ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul> |
| Distribution                              | Vd/F or Vd                                                        | Mean (%CV)                                                                                                              |
|                                           | % bound                                                           | Mean (%CV)                                                                                                              |
| Elimination                               | Route                                                             | <ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>      |
|                                           | Terminal t <sub>1/2</sub>                                         | <ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>         |
|                                           | CL/F or CL                                                        | Mean (%CV)                                                                                                              |
| Intrinsic Factors                         | Age                                                               | Specify mean changes in Cmax and AUC                                                                                    |
|                                           | Sex                                                               | Specify mean changes in Cmax and AUC                                                                                    |
|                                           | Race                                                              | Specify mean changes in Cmax and AUC                                                                                    |
|                                           | Hepatic & Renal Impairment                                        | Specify mean changes in Cmax and AUC                                                                                    |
| Extrinsic Factors                         | Drug interactions                                                 | Include listing of studied DDI studies with mean changes in Cmax and AUC                                                |
|                                           | Food Effects                                                      | Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)                                  |
| Expected High Clinical                    | Describe worst case scenario and expected fold-change in Cmax and |                                                                                                                         |

|                   |                                                                                |
|-------------------|--------------------------------------------------------------------------------|
| Exposure Scenario | AUC. The increase in exposure should be covered by the supra-therapeutic dose. |
|-------------------|--------------------------------------------------------------------------------|

Application  
Type/Number

Submission  
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Submitter Name

Product Name

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NDA-22345

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ORIG-1

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VALEANT  
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LS NORTH  
AMERICA

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RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
11/12/2009



NDA 022345

**NDA ACKNOWLEDGMENT**

Valeant Pharmaceuticals North America  
Attention: Susan T. Hall, Ph.D.  
Senior Vice President, Head of Neurology R&D and RA Compliance  
One Enterprise  
Aliso Viejo, CA 92656

Dear Dr. Hall:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: POTIGA (retigabine) tablets, 50 mg, (b) (4) 200 mg, 300 mg, 400 mg

Date of Application: October 30, 2009

Date of Receipt: October 30, 2009

Our Reference Number: NDA 022345

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 29, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must

be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: [http://internet-dev.fda.gov/cder/regulatory/FDAAA\\_certification.htm](http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm). Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Stephanie N. Keefe  
Regulatory Health Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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ORIG-1

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VALEANT  
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STEPHANIE N KEEFE  
11/12/2009

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|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    | <b>REQUEST FOR CONSULTATION</b>                                                                                                                                                                                      |                                                                             |                                      |
| TO (Division/Office):<br>Division of Biostatistic VI<br>Attention: Karl Lin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    | FROM:<br><b>Russell Katz, MD, Division of Neurology<br/>Products (DNP), HFD-120</b>                                                                                                                                  |                                                                             |                                      |
| DATE<br>November 5, 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | IND NO.                            | NDA NO.<br>22-345                                                                                                                                                                                                    | TYPE OF DOCUMENT<br>New original NME NDAs                                   | DATE OF DOCUMENT<br>October 30, 2009 |
| NAME OF DRUG<br>Potiga (retigabine) tablets                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>1                                                                                                                                                                                          | DESIRED COMPLETION DATE<br>May 30, 2010<br>PDUFA goal date: August 30, 2010 |                                      |
| NAME OF FIRM: Valeant Pharmaceuticals North America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| STATISTICAL EVALUATION BRANCH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    | STATISTICAL APPLICATION BRANCH                                                                                                                                                                                       |                                                                             |                                      |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    | <input type="checkbox"/> CHEMISTRY REVIEW<br><input checked="" type="checkbox"/> PHARMACOLOGY - CAC statistical data<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |                                                                             |                                      |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                                                         |                                                                             |                                      |
| <b>IV. DRUG EXPERIENCE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                    | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS                              |                                                                             |                                      |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    | <input type="checkbox"/> PRECLINICAL                                                                                                                                                                                 |                                                                             |                                      |
| <p><b>REQUEST:</b> NDA 22-345 was received on October 30, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has a PDUFA goal date of 8-30-10. The entire submission may be accessed at : <a href="\\CDSESUB1\EVSPROD\NDA022345\022345.ENX">\\CDSESUB1\EVSPROD\NDA022345\022345.ENX</a>. <b>Please review and comment on the acceptability of the carcinogenicity statistical information submitted in NDA 22-345.</b> The filing meeting for NDA 22-345 is scheduled for 12/15 at 8:30am (WO 22 Rm. 4270) if you or someone from your group would like to attend. Electronic datasets have been provided for both of the carcinogenicity toxicity studies in m4.2.3.4.1.</p>                                                                                                                                                                      |                                    |                                                                                                                                                                                                                      |                                                                             |                                      |
| SIGNATURE OF REQUESTER<br>Stephanie Keefe, Regulatory Project Manager, DNP<br>Food and Drug Administration<br>Phone: 301-796-4098<br>Email: <a href="mailto:stephanie.keefe@fda.hhs.gov">stephanie.keefe@fda.hhs.gov</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                    | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> MAIL <input checked="" type="checkbox"/> Email                                                                                                            |                                                                             |                                      |
| SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    | SIGNATURE OF DELIVERER                                                                                                                                                                                               |                                                                             |                                      |

Application  
Type/Number

Submission  
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Product Name

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NDA-22345

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STEPHANIE N KEEFE  
11/12/2009

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    | <b>REQUEST FOR CONSULTATION</b>                                                                                                                                                                                      |                                                                              |                                      |
| TO (Division/Office):<br>Division of Biostatistic VI<br>Attention: Karl Lin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    | FROM:<br><b>Russell Katz, MD, Division of Neurology<br/>Products (DNP), HFD-120</b>                                                                                                                                  |                                                                              |                                      |
| DATE<br>November 5, 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | IND NO.                            | NDA NO.<br>22-345                                                                                                                                                                                                    | TYPE OF DOCUMENT<br>New original NME NDAs                                    | DATE OF DOCUMENT<br>October 30, 2009 |
| NAME OF DRUG<br>Potiga (retigabine) tablets                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>1                                                                                                                                                                                          | DESIRED COMPLETION DATE<br>Late May 2010<br>PDUFA goal date: August 30, 2010 |                                      |
| NAME OF FIRM: Valeant Pharmaceuticals North America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| STATISTICAL EVALUATION BRANCH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    | STATISTICAL APPLICATION BRANCH                                                                                                                                                                                       |                                                                              |                                      |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    | <input type="checkbox"/> CHEMISTRY REVIEW<br><input checked="" type="checkbox"/> PHARMACOLOGY - CAC statistical data<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |                                                                              |                                      |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                                                         |                                                                              |                                      |
| <b>IV. DRUG EXPERIENCE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                    | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS                              |                                                                              |                                      |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    | <input type="checkbox"/> PRECLINICAL                                                                                                                                                                                 |                                                                              |                                      |
| <p><b>REQUEST:</b> NDA 22-345 was received on October 30, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has been filed and the PDUFA goal date is 8-30-10. Please review and comment on the thorough QT study contained in this submission. The entire submission may be accessed at : <a href="\\CDSESUB1\EVSPROD\NDA022345\022345.ENX">\\CDSESUB1\EVSPROD\NDA022345\022345.ENX</a>. <b>Please review and comment on the acceptability of the carcinogenicity statistical information submitted in NDA 22-345.</b> The filing meeting for NDA 22-345 is scheduled for 12/15 at 8:30am (WO 22 Rm. 4270) if you or someone from your group would like to attend.</p>                                                                                                                                                                           |                                    |                                                                                                                                                                                                                      |                                                                              |                                      |
| SIGNATURE OF REQUESTER<br>Stephanie Keefe, Regulatory Project Manager, DNP<br>Food and Drug Administration<br>Phone: 301-796-4098<br>Email: stephanie.keefe@fda.hhs.gov                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                    | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> MAIL <input checked="" type="checkbox"/> Email                                                                                                            |                                                                              |                                      |
| SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    | SIGNATURE OF DELIVERER                                                                                                                                                                                               |                                                                              |                                      |

Application  
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Submission  
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Submitter Name

Product Name

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NDA-22345

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AMERICA

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RETIGABINE

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/s/  
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STEPHANIE N KEEFE  
11/05/2009

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         | <b>REQUEST FOR CONSULTATION</b>                                                                                         |                                                                                                                                                                                    |                                                                                   |
| TO (Office/Division): <b>Division of Biometrics I</b><br>Attn: <b>Kun Jin, PhD</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         | FROM (Name, Office/Division, and Phone Number of Requestor):<br><b>Russell Katz, MD, Division of Neurology Products</b> |                                                                                                                                                                                    |                                                                                   |
| DATE<br><b>November 4, 2009</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | IND NO. | NDA NO.<br><b>22-345</b>                                                                                                | TYPE OF DOCUMENT<br><b>New NDA/Original Submission</b>                                                                                                                             | DATE OF DOCUMENT<br><b>October 30, 2009</b>                                       |
| NAME OF DRUG<br><b>Potiga (retigabine) tablets</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         | PRIORITY CONSIDERATION<br><b>Standard</b>                                                                               | CLASSIFICATION OF DRUG<br><b>1 (NME)</b>                                                                                                                                           | DESIRED COMPLETION DATE<br><b>May 30, 2010 (PDUFA goal date: August 30, 2010)</b> |
| NAME OF FIRM: <b>Valeant Pharmaceuticals North America</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <input checked="" type="checkbox"/> NEW STANDARD NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <b>IV. DRUG SAFETY</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <input type="checkbox"/> CLINICAL<br><input type="checkbox"/> NONCLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| <b>COMMENTS / SPECIAL INSTRUCTIONS:</b> On October 30, 2009, DNP received a NEW NME NDA (22-345) for Potifa (retigabine) Tablets for the treatment of partial onset seizures. Attached is an electronic link to the NDA 22-345 original application for your review and comment. \\CDSESUB1\EVSPROD\NDA022345\022345.ENX<br>The PDUFA goal date is August 30, 2010; the 45-day filing meeting is December 15, 2009 at 8:30am. Please let me know the review assignment ASAP and advise him/her that the biometrics filing review should be completed prior to the filing meeting. This application is being reviewed according to the 21 <sup>st</sup> Century Review process; therefore, the biometrics review will need to be completed by June 30, 2010 (end of month 8). The assigned clinical reviewer is Steve Dinsmore; the CDTL is Norman Hershkowitz.                                                                                                                                        |         |                                                                                                                         |                                                                                                                                                                                    |                                                                                   |
| SIGNATURE OF REQUESTOR<br><b>Stephanie Keefe, Regulatory Project Manager, DNP</b><br>Food and Drug Administration<br>Phone: 301-796-4098<br>Email: <a href="mailto:stephanie.keefe@fda.hhs.gov">stephanie.keefe@fda.hhs.gov</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |                                                                                                                         | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DARRTS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |                                                                                   |
| PRINTED NAME AND SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                                                                                                         | PRINTED NAME AND SIGNATURE OF DELIVERER                                                                                                                                            |                                                                                   |

Application  
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Product Name

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NDA-22345

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/s/  
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STEPHANIE N KEEFE  
11/12/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): **HFD-710 Division of Biometrics**  
Attn: **Kun Jin, PhD**

FROM (Name, Office/Division, and Phone Number of Requestor):  
**Russell Katz, MD, Division of Neurology Products**

DATE  
**November 4, 2009**

IND NO.

NDA NO.  
**22-345**

TYPE OF DOCUMENT  
**New NDA/Original  
Submission**

DATE OF DOCUMENT  
**10/30/09; rcv'd 11/3/09**

NAME OF DRUG  
**Potiga (retigabine) tablets**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG  
**Partial-Onset Seizures**

DESIRED COMPLETION DATE  
**November**

NAME OF FIRM: **Valeant Pharmaceuticals North America**

### REASON FOR REQUEST

#### I. GENERAL

- |                                                          |                                                  |                                                            |
|----------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |                                                            |

#### II. BIOMETRICS

- |                                                 |                                                            |
|-------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW                  |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY                      |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS                  |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |                                                            |

#### III. BIOPHARMACEUTICS

- |                                                  |                                                      |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |                                                                                    |                                                                              |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |                                                                              |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Attached is a link to the NDA 22-345 original submission for your review and comment. The network location is : \\CDSesub1\EVSPROD\NDA022345\022345.ENX

SIGNATURE OF REQUESTOR  
**Stephanie Keefe, Regulatory Project Manager, DNP**  
Food and Drug Administration  
Phone: 301-796-4098  
Email: [stephanie.keefe@fda.hhs.gov](mailto:stephanie.keefe@fda.hhs.gov)

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22345

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STEPHANIE N KEEFE  
11/04/2009

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         | <b>REQUEST FOR CONSULTATION</b>                                                                                      |                                                                                                                                                                      |                                                |
| TO (Office/Division): <b>OND /Div Cardiology and Renal Products IRT-QT</b><br>Attn: <b>Devi Kozeli (WO22/Room 4183)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         | FROM (Name, Office/Division, and Phone Number of Requestor): <b>Russell Katz, MD, Division of Neurology Products</b> |                                                                                                                                                                      |                                                |
| DATE<br><b>October 5, 2009</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | IND NO. | NDA NO.<br><b>22-345</b>                                                                                             | TYPE OF DOCUMENT<br><b>QT Study Report</b>                                                                                                                           | DATE OF DOCUMENT<br><b>10/30/09</b>            |
| NAME OF DRUG<br><b>Potiga (Retigabine) Tablets</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         | PRIORITY CONSIDERATION<br><b>Standard</b>                                                                            | CLASSIFICATION OF DRUG<br><b>Partial onset-seizures</b>                                                                                                              | DESIRED COMPLETION DATE<br><b>May 30, 2010</b> |
| NAME OF FIRM: <b>Valeant Pharmaceuticals North America</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <input type="checkbox"/> NEW PROTOCOL<br><input checked="" type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILTY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <b>IV. DRUG SAFETY</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <input checked="" type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| <b>COMMENTS / SPECIAL INSTRUCTIONS:</b> NDA 22-345 was received on October 30, 2009 and provides for adjunctive therapy in refractory epilepsy patients with partial-onset seizures. This is a NME. The application has a PDUFA goal date of 8-30-10. Please review and comment on the thorough QT study contained in this submission. The entire submission may be accessed at : \\CDSesub1\EVSPROD\NDA022345\022345.ENX.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |                                                                                                                      |                                                                                                                                                                      |                                                |
| SIGNATURE OF REQUESTOR<br><b>Stephanie Keefe, Regulatory Project Manager, DNP</b><br>Food and Drug Administration<br>Phone: 301-796-4098<br>Email: stephanie.keefe@fda.hhs.gov                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |                                                                                                                      | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |                                                |
| PRINTED NAME AND SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                                                                                                      | PRINTED NAME AND SIGNATURE OF DELIVERER                                                                                                                              |                                                |

Application  
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NDA-22345

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STEPHANIE N KEEFE  
11/12/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 053950

Valeant Pharmaceuticals North America  
ATTENTION: Susan Hall, PhD  
Sr. Vice President, Global Regulatory Sciences & Compliance  
One Enterprise  
Aliso Viejo, California 92656

Dear Dr. Hall:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for retigabine tablets.

We also refer to the telecon between representatives of your firm and the FDA on August 4, 2009. The purpose of the meeting was to discuss several issues that have arisen during the preparation of your New Drug Application which require additional discussion and agreement with the Agency.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dorothy Demczar, PharmD, Regulatory Project Manager at (301) 796-2263.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center of Drug Evaluation and Research

Enclosure - Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** August 4, 2009  
**TIME:** 1:00 – 2:00 PM  
**LOCATION:** Telecon  
**APPLICATION:** IND 53950  
**PRODUCT:** Retigabine tablets  
**SPONSOR:** Valeant Pharmaceuticals  
**TYPE OF MEETING:** Type C  
**MEETING CHAIR:** Russell Katz, MD, Director  
Division of Neurology Products (DNP)  
**MEETING RECORDER:** Dorothy Demczar, PharmD, Regulatory Project Manager

### **FDA ATTENDEES:**

Russell Katz, MD, Director, DNP  
Norman Hershkowitz, MD, Clinical Team Leader, DNP  
Steven Dinsmore, DO, Medical Officer, DNP  
Ed Fisher, PhD Pharmacology/Toxicology Reviewer, DNP  
Lois Freed, PhD Supervisory Pharmacologist, DNP  
Martha Heimann, PhD, Team Leader, CMC  
Tristan Massie, PhD, Biostatistics Reviewer  
Kellie Taylor, PharmD, Team Leader, DMEPA  
Dorothy Demczar, PharmD, Regulatory Project Manager, DNP

### **VALEANT PHARMACEUTICALS AND GLAXOSMITHKLINE ATTENDEES:**

#### **Valeant Pharmaceuticals**

Sue Hall, PhD, Sr. Vice President, Global Regulatory Sciences & Compliance  
Janet Hammond, MD, PhD, Chief Medical Officer and Sr. Vice President Global Medical Affairs  
Tim Hess, Sr. Director, Analytical Development  
Robert Kang, Director, Data Management

#### **GlaxoSmithKline**

Dwayne Campbell, PhD, Manager of Product Development  
Giselle Limentani, PhD, Director, Product Development  
Alan Millar, PhD, Director, Synthetic Chemistry  
Debra Tompson, Principal Pharmacokineticist, Clinical Pharmacology Modelling and Simulation  
Richard Kavoussi, MD, Vice President, Clinical Leader, Neurosciences MDC  
Robin White, Manager, Statistics & Programming  
Mark Baumgartner, Senior Director, US Regulatory Affairs  
Ethnie Conner, Director, Global Pre-Approval, CMC Regulatory Affairs  
Mike Kelly, Director, Safety Assessment  
Chris Kidd, Medicine Process Delivery Leader  
Liz Mitchell, Project Leader

**BACKGROUND:**

In late 2007, Valeant Pharmaceuticals scheduled a pre-NDA meeting with FDA to discuss plans for a new drug application (NDA) for retigabine. Because all questions in Valeant's meeting information package (September 10, 2007; SN 344) had been addressed by FDA's written responses (October 5, 2007), Valeant accepted FDA's suggestion to cancel the pre-NDA meeting scheduled for October 11, 2007. Valeant is currently targeting submission of the NDA for retigabine in October 2009. As outlined in the meeting request dated May 8, 2009, subsequent to formal interactions that occurred in late 2007, several issues have been identified for which Valeant requests FDA feedback prior to completing its NDA for retigabine.

**QUESTIONS AND TOPICS FOR DISCUSSION:**

1. Does the Agency agree with our position that, together with other available nonclinical data, results from the in vivo micronucleus and comet assay qualify the (b) (4) impurity such that the usual thresholds for non-genotoxic impurities under ICH Q3A may be applied?

**FDA Preliminary Response:**

*At this time, we cannot definitively answer this question since the data are still under review. However, it seems unlikely that the negative results in the in vivo assay will outweigh the positive in vitro Ames assay. We would recommend that you continue efforts to reduce the amount of (b) (4) to a level that would result in a daily dose of (b) (4)*

**Meeting discussion:**

The Sponsor presented their approach to dealing with the (b) (4) impurity and requested comments from the Agency regarding this approach, which they said was based on their interpretation of the FDA draft guidance on genotoxic impurities (*Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*). The Division noted that the draft guidance has not been finalized, and some aspects of the guidance are continuing to be discussed internally. The Division noted that the Sponsor's data are currently under review, and that the Genetic Toxicology Subcommittee will be consulted before a final decision is made. The Division noted that if the impurity is considered genotoxic, the threshold is (b) (4) or below for the sum of (b) (4); and the other two structurally related impurities (b) (4). If the Sponsor is ultimately unable to achieve this level, this would be a review issue.

2. Given the minor process modifications described to afford improved impurity and particle size control, does the Agency agree the existing primary stability database remains fully supportive of the commercial process?

**FDA Preliminary Response:**

*We do not agree that the proposed process changes can be considered minor given the change from a (b) (4) process for the final drug substance. The submitted database will be reviewed in support of the proposed drug*

substance retest dating period. The retest dating period will be established based on the extent and quality of the supporting data to be provided in the application.

Additionally, we note that the proposed change from the (b) (4) process may result in changes to the (b) (4) drug substance. We also note differences in the particle size distribution for drug substance batch 02070069, which was used for the bioequivalence study (Study 105) and the batches manufactured using the proposed commercial process. Therefore, you should provide appropriate comparative dissolution profile data for the drug product manufactured using drug substance obtained from (b) (4) the drug product used in clinical studies and manufactured using drug substance obtained using the (b) (4) process.

### **Meeting Discussion**

With respect to stability data, the Sponsor's position is that the existing stability database generated using (b) (4) drug substance represents a "worst-case" based on drug substance purity. The Agency indicated that this is a matter for review.

With respect to the request for comparative dissolution data, the Agency clarified that there was a concern that the (b) (4) processes could result in formation of differing amounts of amorphous material, which might result in differences in dissolution. The Sponsor indicated that it would be able to provide the requested dissolution data for the highest tablet strength, 400 mg.

### **Additional CMC comment:**

In the February 27, 2009 submission, you identify one starting material, (b) (4). (b) (4) Until you have commercial drug substance manufacturing data on the (b) (4) levels of these impurities from a sufficient number of commercial batches that account for typical variations in the manufacturing environment (e.g., personnel and process variability), we recommend that you establish appropriate controls for these impurities in the drug substance or appropriate intermediate specifications or qualify the impurities in appropriate non-clinical studies. We also expect that any future proposal to eliminate testing for these impurities should include your plan to study the impact of future process changes on these impurities.

## **BIOPHARMACEUTICS**

- |                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>3. Valeant and GSK consider that the available data support the therapeutic equivalence of the market image and clinical trial tablets and that the data generated in Study 105 are adequate to allow the NDA to be filed. Does the Agency agree?</p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### **FDA Preliminary Response:**

From an Office of Clinical Pharmacology perspective, this is not considered to be a filing issue since the study to establish the bioequivalence between the TBM formulation and the

*clinical formulation has been conducted. This is, however, a review issue, and the acceptability of the study results will be reviewed at the NDA stage.*

**Meeting discussion:**

NONE

4. As indicated in Section 11.2.4, in order to obtain a greater understanding of the relationship between dissolution and C<sub>max</sub>, an additional pharmacokinetic study will be conducted using clinical tablets containing a lot of drug substance with a particle size more typical of that used in Studies 301 and 303. While Valeant and GSK do not believe the data from this additional pharmacokinetic study are required for approval of the retigabine tablet NDA, the study is anticipated to be completed within the cut off date for the 120-day safety update. Therefore, the study report is currently planned for inclusion in that that submission. Does the Agency agree that results from the additional pharmacokinetic study would not constitute a major amendment and extend the NDA review clock?

**FDA Preliminary Response:**

*We cannot comment at this point on the importance of the results from the additional PK study, nor on whether they are required for the drug approval. If the results of this additional PK study are considered to be crucial for providing supportive evidence to establish the bioequivalence between these two formulations, we recommend that you include the study result in the NDA submission. Please also see our comment to question 3*

**Meeting discussion:**

NONE

CLINICAL

**Safety Data Cut-off**

5. Does FDA agree with the approach outlined for safety data cut off outlined in section 11.3.1?

**FDA Preliminary Response:**

YES

**Meeting discussion:**

NONE

**Proposal for per patient profiles in lieu of narratives**

6. Does FDA agree with the proposed approach to address the Agency's expanded request for narratives for urinary/renal cases via preparation of detailed listings (per patient profiles) as outlined in section 11.3.2?

**FDA Preliminary Response:**

YES

**Meeting discussion:**  
NONE

**Pediatric Plan:**

7. At the end of Phase 2 meeting (November 2, 2004), the Agency agreed with the sponsor's proposal to defer submission of pediatric data. Does the Agency reconfirm its agreement to grant a deferral for submission of data from studies in pediatric patients until after the NDA for adult patients is approved?

**FDA Preliminary Response:**  
YES

**Meeting discussion:**  
NONE

NDA CONTENT/FORMAT RELATED

**Clinical Study Reports:**

8. With regard to the legacy Phase 1 and 2a studies completed by prior sponsors, does the Agency agree that the deviations from ICH E3 content/format described in section 11.4.1 are acceptable?

**FDA Preliminary Response:**  
*YES, but this does not exclude potential problems that may be discovered upon review.  
Please note, we would like all narratives hypertext linked from study reports and CRFs*

**Meeting discussion:**  
NONE

**Foreign Clinical Studies Not Conducted Under an IND:**

9. For legacy Phase 1 and 2 studies, does the Agency agree with the proposal (outlined in section 11.5) to request a waiver for certain provisions of the updated final rule on conditions under which FDA will accept non-IND foreign clinical studies in support of an NDA (21 CFR 312.120 )?

**FDA Preliminary Response:**  
YES

**Meeting discussion:**  
NONE

**Preparation of Electronic Data Sets for Clinical Studies:**

10. Does the Agency agree with the approach described in section 11 to provide datasets for the primary efficacy studies ('205, '301, and '302)?

**FDA Preliminary Response:**

YES

**Meeting discussion:**

NONE

11. Does the Agency agree with the approach described in the meeting information package to provide datasets for all other studies?

**FDA Preliminary Response:**

YES. But, to examine the extent of this you should provide a tabular presentation of the number of patients, medication dose and duration that are represented by the legacy studies as compared to the numbers captured in your current CRO framework. A clear description as to how the datasets were derived from legacy studies should be included.

**Meeting discussion:**

NONE

12. Valeant has constructed datasets as summarized in section 11.4.2 in this briefing package. The key CRT packages, such as the primary efficacy studies, ISS, ISE, and the Population PK report could be made available to the FDA reviewers in advance of the NDA in order to orient them to how the CRTs have been structured and facilitate their review of the NDA. To this end, Valeant would be pleased to work with the Agency to determine exact timings and a process to allow the reviewers to interact with sponsor-identified technical representatives (subject of a separate discussion). Is the Agency interested in a pre-review of the CRT data packages prior to submission of the NDA that is currently targeted for mid-September/mid-October?

**FDA Preliminary Response:**

If review packages are appropriately assembled this should not generally be necessary, however, if there are specific issues regarding the datasets the Division may assist. This should be discussed further at the meeting.

**Meeting discussion:**

NONE – The Sponsor clarified that they had no specific issues for discussion at this time.

**ADDITIONAL DISCUSSION:**

The Sponsor asked to discuss the Agency's request to (b) (4) suggesting a change in the proposed established name for (b) (4). Specifically, the Sponsor asked if there was any

additional comment that the Agency could provide regarding their recent request for clarification surrounding the change in the established name. DMEPA responded that the Agency hasn't had the opportunity to fully discuss the request, internally. A meeting is currently scheduled at the end of this week to discuss the issue and a response will be provided. The Sponsor stated that they are planning to submit additional documentation related to the pharmacokinetics (PK) of the products supporting their position as to why the established name of (b) (4) is acceptable to exist with (b) (4). DMEPA asked, if by PK related, the documentation would support reasons why (b) (4) would not be marketed as a transdermal dosage form and (b) (4) would not be pursued as an oral dosage form. The Sponsor confirmed that this was the case and that the supporting documentation was complete and (at the Agency's request), would be submitted to the Agency prior to the scheduled internal meeting on Friday.

| Linked Applications | Submission Type/Number | Sponsor Name                                    | Drug Name / Subject |
|---------------------|------------------------|-------------------------------------------------|---------------------|
| IND 53950           | GI 1                   | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | GKE-841             |
| IND 53950           | GI 1                   | VALEANT<br>PHARMACEUTICA<br>LS NORTH<br>AMERICA | GKE-841             |

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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  
08/31/2009

**Gilbert, Kristen**

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**From:** Rosenthal, Art L.  
**Sent:** Wednesday, October 10, 2007 9:26 PM  
**To:** Gilbert, Kristen; Allen, Dwain K.  
**Subject:** Fw: IND 53,950; preliminary responses for P-NDA mtg

**Attachments:** PNDA Q&As.pdf



PNDA Q&As.pdf  
(201 KB)

----- Original Message -----

From: Griffis, Melina <melina.griffis@fda.hhs.gov>  
To: Rosenthal, Art L.  
Sent: Sun Oct 07 09:13:20 2007  
Subject: FW: IND 53,950; preliminary responses for P-NDA mtg

Please confirm receipt of this email, I am not sure why you didn't get it the first time.

\*\*\*\*\*  
Melina N. Griffis, R.Ph., CDR-USPHS  
Senior Regulatory Project Manager  
Division of Neurology Products, CDER, FDA  
10903 New Hampshire Ave, Bldg 22, Rm 4355 Silver Spring, MD 20993-0002

Office- 301-796-1078 Fax- 301-796-9842  
Email- melina.griffis@fda.hhs.gov

---

From: Griffis, Melina  
Sent: Friday, October 05, 2007 3:51 PM  
To: 'Rosenthal, Art L.'  
Subject: IND 53,950; preliminary responses for P-NDA mtg

Hi Art,

Per my voicemail, attached are our preliminary response to the questions in your pre-NDA briefing package. As stated the Division feels a meeting is not necessary. Please let me know if your team concurs.

<<PNDA Q&As.pdf>>

\*\*\*\*\*  
Melina N. Griffis, R.Ph., CDR-USPHS  
Senior Regulatory Project Manager  
Division of Neurology Products, CDER, FDA  
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## **SPECIFIC QUESTIONS GROUPED BY DISCIPLINE**

### **4.1 CLINICAL**

- 1) The two ongoing Phase III studies (Studies 301 & 302), along with a previously completed Phase II Study (Study 205), will be submitted in the NDA to support the claim of safety and efficacy for retigabine. The Division previously agreed (at the EOP2 meeting) that the design of Study 205 met the requirements of an adequate and well-controlled clinical trial of the safety and efficacy of retigabine as adjunctive therapy for treatment of partial onset seizures in adults. Additionally, please refer to Valeant's May 13, 2005 "Request for Special Protocol Assessment" (Serial Number 165), as well as the September 1, 2005 "Protocol Amendment: Change in Protocol" (Serial Number 170) and April 17, 2006 "Protocol Amendment: Change in Protocol" (Serial Number 184) to IND 53, 950. Please also refer to the Agency's June 25, 2005 letter and the August 7, 2005 minutes. These correspondences confirm the Agency's acceptance of clinical study protocols 301 and 302, along with clinical study 205, for fulfilling the requirements of adequate and well-controlled clinical trials of the safety and efficacy of retigabine as adjunctive therapy for treatment of partial onset seizures in adults to obtain FDA approval. (See Section 5.6.3, Phase III Studies; Appendix A, FDA Correspondences and Minutes of FDA Meetings; Appendix B, Protocol Synopses; Appendix E, Statistical Analysis Plans.)

**Does the Division confirm that Studies 205 and 301/302 are acceptable as the basis for approval, as agreed at the EOP2 meeting and in the subsequent SPA correspondences?**

**Division Response:** The division stands by the statements documented in the Division's correspondence regarding the end of phase 2 meeting and the special protocol assessment. The three studies generally appear adequate to serve as pivotal trials that will contribute to the final decision on approval. Approval, however, will remain a review issue.

- 2) Study 205 was conducted from 1999 to 2001 in Europe, Australia and in the US in accordance with GCP standards. The Study Report was written by a previous sponsor and the format does not comply with current ICH format. At the EOP2 meeting the design of Study 205 was accepted by the Division as meeting the requirements of an adequate and well controlled clinical trial of the safety and efficacy of retigabine as adjunctive therapy for treatment of partial onset seizures in adults. Therefore, Valeant intends to prepare an ICH format version of the report (to be harmonized with the report format for Studies 301 and 302) and to include it, together with the original version, in the NDA.

**Does the Division concur with this approach to the 205 Study Report?**

**Division Response: Yes**

- 3) As described in further detail in the pre-NDA Briefing Document (Section 5.6.6), Valeant has included the Division's recommendations from the EOP2 meeting on

the population pharmacokinetic analysis (November 2, 2004, see Appendix A) in the Phase III program and in the final population pharmacokinetic strategy. Valeant proposes that a sample collection cut-off date of October 31, 2007 for inclusion of plasma concentration data into the analysis be established. With this cut-off date, Valeant expects that 100% of subjects from Study 301 and approximately 80% of the subjects in Study 302 will have provided on-treatment samples for inclusion in the population analysis. Specifically, this would include 150 subjects from Study 301 and approximately 270 subjects from study 302 for a total of 420 subjects. Thus, the cut-off date will ensure that more than 85% of the patients in the Phase III program will contribute plasma concentration data for the analysis. (For Clinical Development Overview see Section 5.6; The draft Population PK Statistical Analysis Plan is in Appendix E)

**Does the Division agree with this population PK sampling cut-off date and approach?**

**Division Response:** The suggested population PK approach and cut-off date are generally acceptable. The final PK/PD model should be based on the combined index and validation datasets. Please refer to the drug-drug interaction guidance for how to conduct population PK screening for potential drug-drug interactions. Furthermore, you should also explore the exposure-response relationship for efficacy (percent change in total partial seizure frequency from baseline and proportion of responders) similar to your proposal for adverse events.

Additional comments: Please submit the population analysis datasets.

- All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

- 4) As of the planned submission date in mid-2008, Valeant estimates that a total of 1850 human subjects (healthy volunteers and patients with epilepsy) will have been exposed to at least one dose of retigabine and will be included in the NDA submission. Of these, 1350 will be epilepsy patients, with more than 700 patients exposed to retigabine for a minimum of 6 months, and more than 350 patients exposed for a minimum of 12 months. These numbers are higher than the 1564 human subjects communicated to the Division at the EOP2 meeting in which the Division agreed that “the completed and proposed studies should jointly result in adequate patient number and exposure”. (Patient exposure data projected for the time of NDA submission are summarized in section 5.6.5.)

At the time of NDA submission, Valeant expects that the only ongoing studies in adult epilepsy patients with partial-onset seizures will be two open label continuation studies (Studies 303 and 304). Valeant is planning a data cut-off of December 31, 2007 for inclusion of data from these studies in the NDA. This data cut-off date is approximately 8 to 9 months prior to the planned NDA submission date. Additional safety and exposure data will be provided for the Study 303 and 304 subjects in the 120-day safety update submission.

**4a) Does the Division agree that the number of human subjects exposed and the duration of exposure at the time of NDA submission are adequate for the evaluation of the safety of retigabine?**

**4b) Does the Division agree that the proposed December 31, 2007 data cut-off for Study 303 and Study 304 (open-label extension studies) is acceptable?**

**Division Response:** a) Exposure numbers are adequate, as per the ICH, and this division. Exposures in most patients should be within the expected therapeutic range. b) The December, 31, 2007 cut off is acceptable.

5) Valeant believes that retigabine has very modest, if any, abuse potential. To date there have been some reports of clinical effects that may be associated with drugs of abuse in clinical studies with retigabine; these observations have generally been mild or moderate and promptly reversible. In order to better characterize the abuse potential of retigabine, Valeant will provide in the NDA a comprehensive review of the relevant nonclinical and clinical data, and will conduct an abuse potential clinical study. Data that substantiate our current assessment of very modest, if any, abuse potential are presented in this Briefing Document (Appendix F) including: 1) a literature review of KCNQ modulation and abuse; 2) non-clinical studies on withdrawal and reinforcement; 3) review of the unblinded AE database from phases I and II; and 4) information on outcome following overdosage. For the NDA submission, Valeant will update the available information from the scientific literature, relevant nonclinical studies, experience following overdosage, and a systematic survey of our clinical safety database. A synopsis of the clinical abuse potential study is presented in Appendix F. The report for this study will be submitted as part of the 120-day safety update of the NDA.

**Does the Division agree that execution and submission of the clinical abuse potential study presented herein, in conjunction with the nonclinical and clinical data package as outlined in this Briefing Document, will adequately and appropriately address the abuse or withdrawal potential of retigabine?**

**Division Response:** No.

\* Full protocols must be submitted before CSS can assess the study design for completeness. The summaries in the Briefing Document provide too little information on each of the studies for CSS to give adequate scientific and regulatory feedback.

\* CSS is available to review protocols for preclinical and clinical abuse-related studies prior to the initiation of the studies.

\* According to 21 CFR § 314.50 (5) (vii), the Abuse Potential Section of an NDA includes the following:

-- Proposal for scheduling and all scientific data that forms the basis of the proposal

-- Abuse Potential Assessment:

Chemistry (including chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)

Pharmacokinetics and pharmacodynamics (including full data on receptor binding)

Primary data from abuse potential studies in animals and humans

Adverse events in clinical studies related to abuse potential

Integrated summaries of safety and efficacy (ISS and ISE)

Information related to overdose

Prospective assessment of the incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies

## **4.2 Nonclinical**

- 6) The completed and proposed nonclinical studies program (pharmacology, safety pharmacology, and toxicology) was presented in the EOP2 briefing document and discussed at the EOP2 meeting (See Appendix C). In addition to these completed and proposed nonclinical studies, the Agency requested the following two studies:

- A 13-week dog toxicity study on the N-acetyl metabolite of retigabine (NAMR, a major human plasma metabolite but not detected to any significant extent in nonrodent species, namely dog and monkey, evaluated to date) (Appendix C, Section 1.2.1).
- Segment II reproductive toxicity studies in the rat and rabbit at higher doses (summary in Appendix C, Section 1.2.3).

In the NDA, Valeant will present the results of all completed and proposed nonclinical studies as presented and discussed at the EOP2 meeting as well as the two studies listed above.

Valeant will also include in the NDA two carcinogenicity studies as well as the additional NAMR studies subsequently discussed with the Agency. (Appendix C, section 1.2.2).

Valeant believes that this extensive nonclinical safety package will be sufficient for registration of retigabine in the proposed epilepsy indication.

**Does the Division agree that the extensive nonclinical study package for retigabine, supplemented by reports of the additional studies identified at the EOP2 meeting and subsequent discussions with the Agency, should provide adequate support for a successful submission and approval of the NDA in the intended epilepsy indication?**

**Division Response:** The adequacy of the completed non-clinical studies to support the NDA will be a matter of review, and cannot be further addressed at the present time. The need for additional studies will depend in part on the results of the planned follow-up studies of the N-acetyl metabolite (NAMR). Due to the toxicity demonstrated only in the 13-week study of NAMR in dog, the adequacy of the pivotal rodent toxicity studies in terms of the plasma NAMR exposures achieved relative to those expected in humans will also need to be reexamined. In addition, the strength of the data supporting the proposed mechanism underlying the bladder and renal histopathology seen in animal toxicity studies of retigabine will be an important consideration in determining the need for additional nonclinical studies.

### 4.3 Chemistry, Manufacturing, and Controls

- 7) Retigabine tablets are produced in five dosage strengths (50 mg, (b) (4) 200 mg, 300 mg, 400 mg) from a common powder blend. (b) (4)

(b) (4)  
(CMC data and plans are in Appendix D.)

**In light of the data and information submitted, does the Division find this manufacturing process validation plan acceptable?**

**Division Response:** Process validation for solid oral dosage forms is a CGMP issue; therefore, the Division has no comment on this plan. With respect to process evaluation, it is our expectation that you will provide sufficient information regarding manufacturing process development and evaluation studies to support the proposed processes, manufacturing equipment, operating parameters, designation of critical steps or intermediates, and controls for critical steps or intermediates.

- 8) The highest daily administered dose of retigabine in the phase III clinical trials is 1200 mg given in divided doses of 400 mg t.i.d. A 400 mg dosage form of retigabine has not been available during the phase III trials. Patients receiving the 1200 mg daily dose are administered one 300 mg tablet and two 50 mg tablets three times daily. It is the intention of Valeant to obtain approval for a 400 mg tablet.

As mentioned in question 7, retigabine tablets are produced in (b) (4) dose proportional strengths (50 mg, (b) (4) 200 mg, 300 mg, 400 mg) from a common powder blend. (b) (4)

(b) (4). The final marketed formulation (commercial) will be essentially identical to the clinical IND batches with only minor changes in colorants and embossing, essentially identical manufacturing process and the same immediate container/closure system. (Appendix D, Section 3.2.P). Valeant will perform a comparative bioequivalence study of the 400 mg commercial retigabine tablets vs. one 300 mg tablet and two 50 mg tablets used in clinical development to support approval of a 400 mg retigabine tablet dosage strength.

**Does the Division find this bioequivalence study plan acceptable?**

**Division Response:** The proposal for a comparative BE study to bridge between the highest 400 mg and lower 300 mg and 50 mg strength is acceptable.

Additional OCP comments:

1. Since you claim that the film-coated tablets used for Phase 3 clinical studies have been shown to be bioequivalent to the oral capsules used in Phase 2 studies, this study should be included as part of the NDA submission for Agency's review if it is different from the Comp-BA study (3065A1-110-US). In addition, if the capsule formulation used in the Phase 1 studies for PK profiling and DDI differ from those used in Phase 2 studies, you should provide linkage to bridge these two (in vitro data or cross study comparison, etc, as appropriate) in support of the NDA application.

2. Ideally the effects of food should be evaluated with the proposed IR formulation of the highest strength (400 mg) intended to market. You should justify at the NDA stage whether results of the food-effect study with a lower strength (b) (4) capsule formulation is also applicable.

3. As recommended by OCP for the EoP2 meeting, you should assess the induction potential of CYP1A2 first via in vitro investigation. For NDA submission, you should address the inhibition potential for CYP2C8 and P-glycoprotein. Please refer to the Agency's draft guidance for drug interaction studies (<http://www.fda.gov/cder/drug/drugInteractions/default.htm>).

4. An outline of the summary section of the HPBIO section is provided (see appendix B). We request that you provide such a summary section as a review aid for CPB reviewer. At the time of NDA submission you can use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it to the agency as a review aid. This summary section should be submitted electronically with appropriate hyperlinks to the relevant supporting data.

9) Retigabine drug substance polymorphism has been well characterized. The solid state has been shown to occur in <sup>(b) (4)</sup> forms, identified as <sup>(b) (4)</sup>



The sponsor proposes to control the formation of undesired polymorphs in the drug substance by the following means:

- <sup>(b) (4)</sup>
- <sup>(b) (4)</sup>
- <sup>(b) (4)</sup>

**Does the Division consider these measures as appropriate control of the solid state form for the retigabine drug substance?**

**Division Response:** The proposed controls appear appropriate pending review of the NDA.

10) Valeant has conducted up to 36 month real-time stability studies on batches of drug product (retigabine film-coated tablets 50 mg to 400 mg). A regression analysis of the 36 month data indicates that the product is stable and supports a shelf life of at least (b) (4) months (see Appendix D, Attachment 2). There was no evidence of any significant degradation even under accelerated conditions. As discussed at the end of phase II meeting, Valeant has changed manufacturing sites for both the drug substance and drug product. For drug substance stability, Valeant will submit six months data as agreed with the Agency (email correspondence attached in Appendix A). For the drug product, Valeant proposes to have stability data of up to at least six months of real time and accelerated testing at the time of submission, and eighteen months of real time data at the time of approval. These data will be generated on the film-coated tablets manufactured at the proposed plant for commercial production according to the specifications and stability protocols as presented in this briefing document. As previously indicated in questions 7 and 8, the final marketed formulation will be essentially identical to the clinical IND batches (Appendix D, section 3.2.P.8). Valeant proposes a (b) (4) month shelf life based on the previous (b) (4) month real time data as well as the planned stability program for the commercial product.

**Does the Division consider a proposed shelf life of (b) (4) months acceptable?**

**Division Response:** The stability packaged described will be acceptable for filing of the NDA. Assignment of the expiration dating period will be a matter for review. Our decision will be based on the extent and quality of the data for the primary stability batches.

We note that the stability data provided in Appendix D, Attachment 2, was generated using formulation development batches, not the primary registration stability batches. It is our understanding, based on the October 7, 2004 end of Phase 2 meeting, that the necessary stability data for the NDA submission will be based on ICH recommendations. Therefore, the designation of drug product batches as primary stability batches should be consistent with the number of batches and batch selection criteria discussed in the ICH guidance *Q1A(R2) Stability Testing of New Drug Substances and Products*. We note that the commercial image tablets may differ from the primary stability batches with respect to film-coat color and debossing. You should, therefore, provide appropriate data, e.g., batch analysis data including comparative dissolution profiles, to demonstrate that the properties of the primary stability batches are comparable to the to-be-marketed tablets. Stability data generated using developmental batches will be considered as supportive data only.

Additional stability data may be submitted during the NDA review. Additional data received within the first 5 months after submission of the NDA will be reviewed as part of the original application; however data received later may not be reviewed during the same review cycle.

#### 4.4 Biostatistics and Programming

Please note that the Statistical Analysis Plans (SAP) for the retigabine Phase III clinical studies 301 and 302 were submitted on November 13, 2006 as Serial Numbers 209 and 210. Pursuant to the email dated June 21, 2007 from Melina Griffis, Senior Regulatory Project Manager, Division of Neurology Products, the statistical reviewer deemed these SAPs to be acceptable. The email correspondence is included in Appendix A.

- 11) The draft Integrated Summary of Efficacy (ISE) Statistical Analysis Plan (SAP) is included as Appendix E, Section 2.

**Does the Division agree that the proposed ISE SAP is adequate?**

**Division Response:** This is adequate

- 12) The draft Integrated Summary of Safety (ISS) Statistical Analysis Plan (SAP) is included as Appendix E, Section 3.

**Does the Division agree that the proposed ISS SAP is adequate?**

**Division Response:** This Division has examined the outline of the ISS. The Sponsor should refer to Appendix A for a listing of the general elements that should appear in the ISS. The Division has the following specific comments on the outline of the ISS provided by the Sponsor:

- The Sponsor notes that EKG parameters 48 hours out from a last dose will be removed from analyses. This should not be done if there is significant drug or metabolites present at this time. In such a case these data can be presented separately.
- Because the division is very interested in the issue of urinary retention and renal system pathology, this section should extensively analyze all relevant data with correlation to animal studies. Nephrologists should be employed to help analyze these data.
- Critical values are presented for selected chemistry lab values. This listing is not complete and must contain all measured values: e.g. electrolytes calcium etc.
- Critical values are presented for blood pressure changes. To be included patients must meet both absolute and change parameters. A separate analysis should be performed for each type of change, i.e. absolute and change from baseline should be analyzed and tabulated separately. Also, orthostatic changes were examined in some protocols. Critical values for orthostatic changes in blood pressure and heart rate should be included.
- Critical values for QT should be presented in terms of QTc, not absolute QT. These should not only include an analysis of absolute values but also change in value (i.e. >30 msec and >60 msec). If PR and QRS are identified as potentially being effected, an analysis of critical values for these parameters should be included.

13) Valeant intends to submit all integrated electronic datasets in SAS System XPORT transport format (version 9 SAS transport files).

**Does the Division have any comment regarding the planned use of SAS version 9?**

**Division Response:** This is adequate

#### **4.5 Submission Logistics**

14) The retigabine NDA will be submitted in eCTD format, which is being developed in accordance with applicable guidance documents. Valeant is collaborating on the electronic submission components with [REDACTED]<sup>(b) (4)</sup>, who plan to communicate directly with the FDA Office of Business Process Support on behalf of Valeant regarding the eCTD technical requirements and participation in the eCTD pilot.

**Does the Division have any comment on this approach?**

**Division Response:** This is adequate

15) Because CRFs and narratives for patients with SAEs, discontinuations due to AEs, and deaths are included in each Clinical Study Report, separate patient profiles will not be submitted in the NDA.

**Does the Division concur with this approach?**

**Division Response:** The divisions would like all narrations to be included in the ISS appendix as a single pdf file. Every narration should be hypertext linked to its CRF. It has recently come to the division's attention that a case of urinary retention was not submitted as an expedited report because it was not deemed as serious. In examination of the information provided on this case, this division would consider this case to be serious. We therefore request that a narration be provided on all significant renal/urinary cases or urinary/renal cases that are described as having severe symptoms.

## Appendix A:

### General elements that should be included in the ISS.

- *The ISS should clearly state what safety assessments were carried out in each study included in the ISS. A tabular presentation of schedule of events might be helpful.*
- *All deaths that occurred in the clinical development program or found during a literature search and from various commercial and non-commercial databases (ex AERS) should be described in a single section and individual deaths should be listed in a table.*
- *All non-fatal serious adverse events, regardless of assigned causality, that occurred during the clinical development program or were reported from secondary sources (i.e. literature and/or post marketing reports) should be described in a single section. Serious adverse events may, in addition to signs, symptoms, and diagnosable events, include changes in laboratory parameters, vital signs, ECG, or other parameters of sufficient magnitude to meet the regulatory definition of a serious adverse event [21 CFR 312.32(a); 314.80(a)].*
- *Dropouts due to adverse events should be clearly described in a single section of the ISS. CRF/narratives should be provided for all dropouts. An overall profile of these patients by reason for dropping out (e.g. adverse events, treatment failures, lost to follow up) should be provided. For the more common adverse events associated with dropouts, the ISS should present the incidence of these adverse events, preferably in a table. Investigator causality assessment can be described but should be justified. The ISS should also describe any dose-response, time dependency of the dropout, drug-demographic, drug-disease, and drug-drug interactions. With respect to rarer events that could represent an important adverse event, the ISS should critically assess whether any of these may represent treatment-induced injury. Finally the ISS should consider these events individually with narratives and reference to other data as appropriate.*
- *The ISS should contain a section entitled "Other Significant Adverse Events." This section should describe significant safety findings such as marked hematological or other lab abnormalities not meeting the definition of serious, any events that led to an adverse dropout or any other intervention such as dose reduction or significant additional concomitant therapy (an expansion of the adverse dropout concept) and potentially important abnormalities not meeting the above definition of serious and not leading to death or modification of therapy (e.g., a single seizure, syncopal episode, orthostatic symptoms). Those adverse events that did not lead to discontinuation but otherwise meet the definition described above should be described in this section.*
- *If preclinical pharmacology/toxicology, post-marketing and/or literature reports provide insight into possible safety signals with the investigational drug product the ISS should describe any findings relative to these signals. This is especially important for new chemical entities. Similarly, if there are particular safety concerns evident from other drug products that are members of the same pharmacological class as the*

*investigational drug product, the ISS should describe a thorough safety analysis of these concerns.*

- *The ISS should contain a section entitled “Common Adverse Events”. You should include a table (or tables) that presents the best overall display of commonly occurring adverse events, generally those occurring at a rate of 1% or more (but lower rates can be presented for very large data bases). This table or tables will be the basis for the ADR table in labeling, which may, however, use a higher cut off if this does not lose important information, and will eliminate ADRs that are equally common on drug and placebo. This table or tables should compare the incidence of common adverse events between cohorts regardless of the investigator’s assignment of causality from the pooled studies. You should justify any decision for not including a particular study in the pooled adverse event incidence tables. For development programs with a significant amount of severe adverse events it would be helpful to include a table that compares the incidence of severe adverse events between cohorts from the pooled studies.*
- *For adverse events that seem clearly drug related (i.e., consistent difference from control across studies, evidence of dose response etc.) you should provide the following additional analysis as appropriate:*
  1. *exploration for dose dependency, exploration of time to onset (for those that show a delay in onset)*
  2. *exploration of adaptation (for common, troublesome events such as somnolence, nausea)*
  3. *explorations of demographic interactions, explorations of drug-disease and drug-drug interactions (if there is a strong signal for an interaction, or a good rationale for expecting an interaction)*
  4. *selective exploration of individual cases in an attempt to better characterize the events.*
- *For each trial described in the ISS you should include a brief discussion on how adverse events were captured (i.e. checklist, open-ended questions on follow up visits etc.). The frequency of assessments should also be described.*
- *For each trial described in the ISS you should clearly state which translation dictionary (MedDRA, COSTART) was used to categorize verbatim adverse event terms.*
- *The ISS should include a discussion of the less common adverse events of significant concern seen across all studies in the clinical development program. Since the overall database is typically very heterogeneous, it is unlikely to lend itself to meaningful estimations of rates or assessments of causality. Thus it may be sufficient to group these events by incidence and by body system. For example, it may be useful to categorize less common adverse events in order of decreasing frequency within certain ranges: e.g.  $\leq 1\%$ , between 0.1% and 1%;  $\leq 0.1\%$ .*
- *The ISS should clearly provide an overview of what laboratory testing (chemistry, hematology, and urinalysis) was carried out in each study. It is best to summarize the overall approach, rather than provide detailed comments about laboratory testing for each study. The ISS should also describe any discrepancies between planned analyses and those actually conducted, as well as the procedures used to evaluate abnormal*

values. Provide a summary table identifying the numbers of patients exposed to test drug who had baseline laboratory values and follow-up assessments.

- The ISS should include an integrated discussion of significant laboratory findings from the clinical development program. Controlled comparisons generally provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. However placebo-controlled trials are generally short term, and unsuitable for assessing late-developing abnormalities, so that longer term data need to be therefore examined also. If there is no concomitant control in the long term studies the comparison may need to be with similar populations outside the NDA. The ISS should explain which studies were pooled relative to the evaluation of laboratory findings and why they were selected.
- The ISS should generally include three standard approaches to the analysis of laboratory data. The first two analyses are based on comparative trial data. The third analysis should focus on all patients in the phase 2-3 experience. Analyses are intended to be descriptive and should not be thought of as hypothesis testing. P-values or confidence intervals can provide some evidence of the strength of the finding, but unless the trials are designed for hypothesis testing (rarely the case), these should be thought of as descriptive. The analysis of all laboratory findings should include a comparative description of mean or median changes from baseline across treatment groups. The ISS should include a discussion on individual patients whose laboratory values deviate substantially from the reference range and describe what criteria were used to identify outliers. Additional analyses may be appropriate for certain laboratory findings, including analyses for dose dependency, time dependency, and also drug-demographic, drug-disease, and drug-drug interactions. The ISS should discuss the rationale for additional explorations, the methods used, and the results and interpretations.
- The ISS should include an evaluation of vital sign assessment using a similar approach as described for laboratory data (i.e, description of vital sign assessment in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers etc).
- The ISS should include an evaluation of ECG findings using a similar approach as described for laboratory data (i.e, description of ECG assessments in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers etc). Particular attention should be given to ECG findings where the timing of the assessment was done at or near the time of maximum concentration for the drug product (generally during phase I or phase II studies) in order to assess QT prolongation effects. A brief discussion on any preclinical cardiac findings would be helpful in orienting the reviewer to any potential concerns.
- The ISS should include a discussion of the impact of immunogenicity (if applicable) on safety, efficacy and/or clinical pharmacology and pharmacokinetics.
- The ISS should include a brief discussion of human carcinogenicity data if available. A systematic discussion of all human tumors reported during drug development can provide useful safety information, particularly in the case of drugs or biologics that have positive genotoxicity or animal carcinogenicity findings, or those that are known immune modulators.

- *The ISS should include a summary of any studies designed to evaluate a specific safety concern(s). These studies may include:*
  1. *studies to assess whether a drug has safety concerns common to its pharmacological class*
  2. *studies in topical products to assess cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity*
  3. *studies to characterize the effect on the QT interval (part of most modern development efforts)*
  4. *studies intended to demonstrate a safety advantage over therapeutic alternatives*
- *The ISS should contain a discussion of abuse potential and any apparent withdrawal symptoms seen during the clinical development program. This discussion should contain a summary of findings from any non-clinical and clinical abuse liability studies (if done), problems in medication accounting encountered while monitoring the investigational supply of medication, chemistry and pharmacology issues that relate to abuse potential, and relevant adverse events and epidemiologic data. The ISS should describe any adverse events that emerge after discontinuation of the drug in order to determine whether they may indicate a withdrawal phenomenon. If studies evaluated the potential for withdrawal phenomena, the ISS should indicate whether there was a prospective or post-hoc assessment of withdrawal emergent signs and symptoms (during drug taper or following discontinuation) and discuss the implications of the approach used on the reliability of the findings.*
- *The ISS should include a discussion of all pregnancies that occur during the clinical development program. A brief description of each pregnancy should include outcome, duration on therapy, use of drug relative to trimester.*
- *The ISS should summarize all overdose experience with the investigational drug/biologic in humans. The summary should include a description of the constellation of signs and symptoms that might be associated with overdose. A description of phase I or phase II safety findings in subjects exposed to doses higher than planned for marketing should be included. Patients with certain physiological differences that would compromise their ability to clear the drug (e.g. renal impairment, limited CYP450 2D6 activity for a drug cleared by this isozyme) may provide relevant data to the clinical implications of overdose.*
- *The ISS should include relevant findings from U.S. and foreign post-marketing experience if available.*
- *The ISS should include a clear description of all patient exposures from the entire clinical development program. The exposure summary should describe various demographic subsets such as race, gender and age. Additionally the summary should include a clear description of dose and duration of exposure. Tables and graphs may be helpful in describing the data sources for the ISS. If applicable the ISS should describe any secondary sources of safety data (ex. studies not conducted under the IND and not meeting the standards for inclusion as primary, post marketing data, and/or literature reports). Secondary sources should be briefly described. Original articles and study reports should be provided.*
- *The ISS should briefly describe the findings from any preclinical studies that were conducted in order to explore certain potential adverse events, using preclinical models based either on a drug's pharmacology or on clinical findings that emerged*

early in clinical development. For example, for a drug anticipated to cause QT prolongation because of its drug class or because QT prolongation was seen in phase 1 studies, were there any preclinical (in-vitro) studies done to evaluate this potential.

- The ISS should include a discussion of any in vitro and in vivo studies done to evaluate how a drug is metabolized and excreted. Issues to be included should include the following:
  1. The enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins.
  2. The effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds.
  3. The major potential safety consequences of drug-drug interactions.
- The ISS should describe the general methodology used to construct the integrated safety review. This discussion should include a rationale for pooling safety data (if done) and the method employed. For example a justification for pooling safety data may include an argument that a larger data base will permit explorations of possible drug-demographic or drug-disease interactions in subgroups of the population or pooling data from different studies can improve the precision of an incidence estimate (i.e., narrow the confidence intervals by enlarging the sample size). In pooling safety data, usually the numerator events and denominators for the selected studies are simply combined. If other more formal weighting methods are used (e.g., weighting studies on the basis of study size or inversely to their variance) the ISS should justify why and how it was done. Information on baseline risk factors of concern should be retrievable from the case report tabulations.
- Since adverse reaction rates may differ considerably from one patient population to another and may change over time the ISS should explore factors that may affect the safety profile of a drug. For example the ISS could explore common drug related predictive factors, such as dose, plasma level, duration of treatment and concomitant medications, and patient related predictive factors such as age, sex, race, concomitant illnesses. In general, these explorations are meaningful only for adverse reactions that appear to be drug-related. The ISS may present these explorations using the following subheadings: exploration of dose-dependency for adverse findings, explorations for time dependency for adverse findings, exploration for drug-demographic interactions, exploration for drug-disease interactions and exploration for drug drug interactions. It may be helpful to link individual safety observations with other on-therapy data such as dose, duration of treatment, concomitant therapy, other adverse effects, lab data or effectiveness results.

# **CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

## **AID (Appendix B)**

**This is only an example of the requested review aid. This can also replace the summary section of Clinical Pharmacology and Biopharmaceutics:**

- **Please fill the headings as it applies to your drug**
- **Additional specific headings can be included to suit the development of your drug/ dosage form (for e.g. For extended release products, headings like comparability of the ER to IR product, for transdermal products section on effect of application site on the PK and adhesiveness of the product etc should be included)**
- **All statements in this summary section should be annotated with links similar to your “annotated label” that would allow the reader to locate all relevant data supporting the statement. Additional links should be provided, whenever possible, for the study report and any raw data located in a SAS transport file or other format that supports the QBR statement.**
- **Within the summary section text, relevant Tables and Figures to understand the data should be included and should not be referred to some Appendix.**
- **Results from various studies, pop pk analyses should be pooled to provide information under each heading, so that consistencies across studies can be determined. If results from two similar studies are different, plausible explanations of these differences should be included.**
- **If different formulations were used during the development, the section should mention what**

**formulation was used (to-be marketed vs. clinical service formulation)**

**1.0 GENERAL ATTRIBUTES OF THE DRUG**

This section contains background information about the drug and drug product to provide a context for assessing the results of the clinical pharmacology and biopharmaceutics studies.

**4.5.1 1.1 Drug/Drug Product Information:**

Dosage Form/Strengths:

Pharmacologic Class:

4.5.1.1.1.1 Chemical Name:

Physical Characteristics:

Formulation: Quantitative formula for all the dose strengths

| Ingredients | Wt (mg/capsule)                                   |  |  |  |  |  |  |  |
|-------------|---------------------------------------------------|--|--|--|--|--|--|--|
|             | <i>1.1.1.1.1.1 Formulation #/Capsule Strength</i> |  |  |  |  |  |  |  |
|             |                                                   |  |  |  |  |  |  |  |
|             |                                                   |  |  |  |  |  |  |  |
|             |                                                   |  |  |  |  |  |  |  |
|             |                                                   |  |  |  |  |  |  |  |
|             |                                                   |  |  |  |  |  |  |  |
|             |                                                   |  |  |  |  |  |  |  |
| Total Size  |                                                   |  |  |  |  |  |  |  |

**1.2 Proposed mechanism(s) of action and indication(s)**

**1.3 Proposed dosage(s) and route(s) of administration?**

## 4.6 2.0 GENERAL CLINICAL PHARMACOLOGY

### 2.1 Design features of the clinical pharmacology and clinical studies used to support dosing or claims:

Here describe the type of pivotal clinical studies in brief for each indication.

For treatment of A: For e.g.

The efficacy of Drug X in patients was established in X Phase 3 randomized, double-blind, parallel, placebo-controlled multi-center trials of Y weeks duration conducted as Z treatment of patients. Of these Z studies only Y studies used the proposed dosing regimen. The X mg/day dose was not replicated in any study. Should use key studies and supportive studies that are used for labeling the product.

Short tabular descriptions may be useful here, for example:

| Protocol | N | Duration | Population | X Dose                    |
|----------|---|----------|------------|---------------------------|
| 101      |   |          |            | PER DAY AND OR BID OR TID |
| 102      |   |          |            | e.g., X MG/DAY            |
| 103      |   |          |            |                           |

Should repeat this information for each indication if multiple indications are proposed.

### 2.2. Clinical endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies

For treatment of A: For e.g.

The primary criterion to establish the efficacy of Drug X was the .....

The primary efficacy parameter was:

The secondary efficacy parameters were:

### 2.3 Exposure-response relationships

### **2.3.1 Characteristics of exposure/effectiveness relationship**

For Efficacy in patients with Y:

An exposure (dose)-response analysis was conducted in Y patients pooled from X studies (Study numbers). Provide exposure or dose/response analyses data. This section should include information on all proposed doses and should also include relevant Tables and Figures of dose-response or exposure-response either from the PK-PD study conducted or from pivotal clinical trials that were used to label the drug product.

This section should also include information on any differences of exposure/dose – response for covariates such as dose, regimen, gender, age, race etc.

### **2.3.2 Characteristics of the exposure-response relationships for safety (dose-response, concentration-response)**

If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

This section should include relevant safety information on all proposed doses and should also include relevant Tables and Figures.

This section should also include information on any differences of exposure/dose – response relationship for safety in covariates such as dose, regimen, gender, age, race etc.

e.g. Dizziness and somnolence were the most prevalent adverse events associated with treatment.

The probability for a subject to experience dizziness (AE1) increased with the dose. At the X mg/day, the incidence of AE1 averaged to be approximately 30% (range: from >20% to <50%). Female patients apparently reported higher incidence of dizziness. It is clear that the variability was high among various trials as shown in the following figure (). The ED<sub>50</sub> for incidence of dizziness was estimated to be X ± Z mg/day. ED50 for severity of somnolence was estimated to be Y ± Z mg/day.

The incidence and severity of AE1 can also be depicted by the following figures that differentiate the incidence of adverse events for the BID and TID regimens.

### **2.3.3 Effect on QT or QTc interval**

Should include relevant Tables and figure showing Concentration-QTc relationship.

**2.3.4 Justification of dose and dosing regimen based on known relationship between dose-concentration-response (In some cases, it may be possible to combine this with 2.3.2 and 2.3.3.)**

The following are the sponsor proposed dosage regimen for .....patients:

| Patient Population | Age Group | Starting Dose | Maximum Dose | Increments |
|--------------------|-----------|---------------|--------------|------------|
| A                  |           |               |              |            |
| B                  |           |               |              |            |

Age Group:

This section should include what information is available for justifying the dose in a particular age group.

Regimen:

**From a pharmacokinetic perspective:**

Based on a half-life of x hours, .....appears to be suitable for the Y regimen. However, the sponsor has conducted pharmacokinetic studies to show that X mg q8h vs. Y mg q12h showed similar pharmacokinetic profiles.

Include figure where possible

Figure: Pharmacokinetics over one dosing interval

Differences in steady state plasma concentration versus time profiles for q8h and q12h dosing regimens can also be evaluated by comparing the differences in  $C_{maxss}$  and  $C_{minss}$  for these two dosing regimens. As the dosing interval is increased from q8h to q12h, the fluctuation between  $C_{maxss}$  and  $C_{minss}$  would be expected to increase, while  $C_{ave}$  would be expected to remain constant. The following figure illustrates that the differences between regimens are small when individual and mean steady-state  $C_{maxss}$ ,  $C_{minss}$ , and  $C_{ave}$  values are compared following a dose of Y mg/day administered q8h and q12h in healthy subjects.

Include figures and Tables as necessary

**From a pharmacodynamic perspective:**

Include figures and Tables justifying the dose and regimen from a efficacy standpoint. Should include information on other regimens studied, but not selected for dosing recommendations and reasons why. This information can be obtained from efficacy studies, PK-PD analysis if conducted or simulation performed.

Conclusions from such analyses must be included. For e.g

These figures show that doses Y mg and above may perform better than the lowest recommended dose in patients based on the EC50 values. However, titrating with a lower dose is desirable for tolerability reasons.

These also show that both X/day and Y/day doses may be acceptable, however, for practical administration reasons X/day may be the preferred choice.

Summary efficacy Tables such as the following should be included.

| <b>Study - Summary of RRatio analysis (ITT)</b> |          |                                |               |                   |
|-------------------------------------------------|----------|--------------------------------|---------------|-------------------|
| <b>Treatment group</b>                          | <b>N</b> | <b>Treatment differences**</b> |               | <b>P value***</b> |
|                                                 |          | <b>Mean (SE)</b>               | <b>95% CI</b> |                   |
|                                                 |          |                                |               |                   |
|                                                 |          |                                |               |                   |
|                                                 |          |                                |               |                   |
|                                                 |          |                                |               |                   |

\* Statistically significant based on Hochberg's procedure (p 0.049).

\*\* Based on treatment means for the raw RRatio

\*\*\* Hochberg procedure applied to the ranked RRatio

| <b>Summary of secondary endpoints (ITT)</b> |                |                           |            |            |            |            |            |
|---------------------------------------------|----------------|---------------------------|------------|------------|------------|------------|------------|
| <b>Study</b>                                | <b>Placebo</b> | <b>X dose and regimen</b> |            |            |            |            |            |
|                                             |                | <b>BID</b>                | <b>BID</b> | <b>TID</b> | <b>BID</b> | <b>BID</b> | <b>TID</b> |
|                                             |                |                           |            |            |            |            |            |
|                                             |                |                           |            |            |            |            |            |
|                                             |                |                           |            |            |            |            |            |
|                                             |                |                           |            |            |            |            |            |
|                                             |                |                           |            |            |            |            |            |

\*statistical significance for difference between X dose and placebo (and/or 95% CI exclude zero for Median change figures)

\*\*subject numbers for ITT population are constant across secondary parameters in this table

**From a safety perspective:**

The two main adverse events of dizziness and somnolence was evaluated in terms of various doses given X/day and Y/day conditioned on severity of the adverse event. The following plots show that Y/day regimen had higher percent of observation for both

dizziness and somnolence. This could be due to sustained concentration of Drug X with Y dosing.

#### Titration Scheme:

If a titration scheme is recommended information relevant to its selection should be included.

### **2.4 PK characteristics of the drug and its major metabolite?**

#### **2.4.1 Single dose and multiple dose PK pharmacokinetics?**

Here Provide tables and figures on mean pharmacokinetic parameters and refer to them in the subsequent sections.

Also include in this section whether the pharmacokinetics of the drug change with chronic dose. And information on whether the multiple dose PK is predicted from single dose PK, accumulation ratio, time to reach steady state etc

#### **2.4.2 General ADME characteristics of the drug**

Absorption: may include information on transporter as well

Distribution: include information on protein binding etc

Metabolism:

Elimination:

#### **2.4.3 Fate of drug as seen in mass balance studies**

Include tables and figures from the mass balance study, also state whether these studies suggest renal or hepatic as the major route of elimination.

#### **2.4.4 Comparison on PK between healthy subjects and patients**

This section should also include information obtained from population analysis if conducted along with any definitive PK study conducted. Table and figures showing the differences in the two population should be included.

#### **2.4.5 Degree of linearity or nonlinearity in the dose-concentration relationship**

The non-linearity can be due to multiple dosing or due to increase of doses. Both should be described in this section.

This section must include Tables showing dose proportionality with statistical evaluation of the data using power model analysis.

This section should also include figures of dose normalized PK parameters versus dose for all relevant PK parameters.

An example Table given below:

Multiple dosing Day 1 vs Day 10 --X-Y mg/day.

| Table                                                                                            |     |     |                            |                                                                               |
|--------------------------------------------------------------------------------------------------|-----|-----|----------------------------|-------------------------------------------------------------------------------|
| Study - Summary Results of the Assessment of Dose Proportionality Using the Power Model Analysis |     |     |                            |                                                                               |
| PK Parameter                                                                                     | Day | AUC | $\beta$ Estimate (95% CI)* | R- Estimate of the Increase in Doses Required for Doubling the AUC (95% CI)** |
|                                                                                                  |     |     |                            |                                                                               |

\* ANOVA (SAS GLM Procedure)

The results of the analysis demonstrate dose proportionality in AUC.

#### 2.4.5 Inter-subject variability in PK parameter

Include Tables to show variability, information from different studies should be included This section should also mention the possible causes of this variability.

### 4.7

## 4.8 3.0 INTRINSIC FACTORS

In the introductory paragraph of this section highlight the key intrinsic factors that influence exposure and/response and what is the impact of such differences in efficacy and safety.

The following intrinsic factors should be discussed:

#### 4.8.1

#### 4.8.2 3.1 Effect of Renal Impairment:

This section should include information on the type of data available, can be presented in Tables such as....

| Group Creatinine Clearance* | Renal function      | N |
|-----------------------------|---------------------|---|
| 1 > 80 mL/min               | Normal              | 8 |
| 2 50-80 mL/min              | Mildly              | 8 |
| 3 30-49 mL/min              | Moderately impaired | 8 |

\* according to Cockcroft and Gault

Include relevant figures and Tables showing the renal clearance with change of creatinine clearance. Include 90% CI in the Tables.

Dosage Adjustment: State if needed or not, If yes then what

Dosing recommendations should be provided in Tabulate format

**Sponsor's Proposal for Dosage Adjustment Based on Renal Function**

| Creatinine Clearance (CLcr)<br>(mL/min) | Total X Daily Dose <sup>a</sup> |                          | Dose Regimen |
|-----------------------------------------|---------------------------------|--------------------------|--------------|
|                                         | Starting dose<br>(mg/day)       | Maximum dose<br>(mg/day) |              |
|                                         |                                 |                          |              |
|                                         |                                 |                          |              |
|                                         |                                 |                          |              |
|                                         |                                 |                          |              |
|                                         |                                 |                          |              |
|                                         |                                 |                          |              |

BID = Two divided doses; QD = Single daily dose.

<sup>a</sup> Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

<sup>b</sup> Supplementary dose is a single additional dose.

**4.8.3 3.2 Effect of Hepatic Impairment:**

information same as above should be included

**4.8.4 3.3 Effect of age:**

Elderly:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

Pediatrics:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

#### **4.8.5 3.4 Effect of Gender:**

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

#### **4.8.6 3.5 Effect of Race:**

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

#### **4.8.7 3.6 . Effect of pregnancy or lactation:**

Similar information as above, if no information available state so.

### **4.9 4.0 EXTRINSIC FACTORS**

In the introductory paragraph of this section highlight the key extrinsic factors (such as herbal, diet, smoking, alcohol) that influence exposure and/response and what is the impact of such differences in efficacy and safety.

Also indicate in brief whether there are any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered.

#### **4.1 In vitro basis of drug interactions**

Include information on the following, this section should not be descriptive only but should include relevant Tables to show the results and indicate which of these can lead to possible in vivo drug interactions under each of these sub headings:

- Drug as substrate of CYP 450
- Drug as inhibitor of CYP 450
- Drug as inducer of CYP 450
- Drug interaction based on protein binding
- Drug as substrate of p-glycoprotein
- Drug as inhibitor of p-glycoprotein
- Any other transporter involved

This section can also include information from mass balance studies that suggest possible interaction, for e.g if totally renally eliminated then there is a possibility of an interaction with drugs that are also renally eliminated.

Also indicate whether the in vitro studies are conducted at relevant therapeutic concentrations (in the same units as for the plasma data (e.g. ng/ml as opposed to  $\mu\text{M}$  or  $\mu\text{mole/liter}$ )).

#### 4.2 In vivo drug interactions

Give a tabular listing of all drugs and indicate whether a dosage adjustment is necessary. This section can be subdivided into pharmacokinetic and pharmacodynamic interactions.

##### Pharmacokinetic Interactions:

For e.g. Influence of Drug X on the pharmacokinetics of concomitant drugs and the influence of these drugs on the pharmacokinetics of Drug X is summarized in the following Table:

| Concomitant Medication | doses evaluated | Drug X on Co-Med PK | Co-Med on Drug X PK | Evaluation Method | Dosage Adjustment |
|------------------------|-----------------|---------------------|---------------------|-------------------|-------------------|
|                        |                 |                     |                     |                   |                   |
|                        |                 |                     |                     |                   |                   |
|                        |                 |                     |                     |                   |                   |
|                        |                 |                     |                     |                   |                   |
|                        |                 |                     |                     |                   |                   |
|                        |                 |                     |                     |                   |                   |
|                        |                 |                     |                     |                   |                   |
|                        |                 |                     |                     |                   |                   |

##### Pharmacodynamic interactions:

List any pharmacodynamic interactions observed, if any.

## 4.10 5.0 GENERAL BIOPHARMACEUTICS

### 4.10.1 5.1 BCS Classification of the drug

This section should include information on solubility, permeability and dissolution of the drug product, which are the basis of classifying the drug and formulation.

All relevant Tables and figures should be included.

### 5.2 Relative Bioavailability of the to-be marketed formulation to those used in the clinical studies

This section should include Tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

If the formulations are not bioequivalent this section should also indicate what safety and efficacy issues may arise, if any. In case of failed BE studies, this section should provide other supporting data regarding the to-be-marketed formulation that would aid in the decision making for the approval of the product.

### 5.3 Absolute Bioavailability and Relative Bioavailability to other dosage forms/route of administrations

This section should include Tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

### 5.4 Food effect

Provide Tables as well showing the ratios and 90% CI. Also indicate if type of meal (light, medium, high) has an effect, if necessary.

Also provide the dosing recommendations based on the results of the Food Effect study. Indication if clinical trials were done with or without regard to food. If different across studies tabular listing of clinical studies and their dosing administration in relation to meals. Include any population analysis data if available.

If a fed BE study was conducted, provide justification for doing so, that will help reviewers in decision making.

### 5.5 Dissolution and IVIVC if appropriate

This section should include dissolution method and specifications and justification for selecting the method (for example stirring speed, media etc).

### 5.6 Alcohol Effect (for ER products):

This is to rule out dose dumping. Should provide the data in tabular format based on in vitro dissolution in different concentrations of alcohol. If in vivo data are available, include in this section as well.

### 4.11 6.0 ANALYTICAL

This section should highlight the method used in analytical assays and provide its validation parameters. This can be done in a tabular format.

| <b>Parameter</b>                 | parent   | -metabolite |
|----------------------------------|----------|-------------|
| Method                           | LC/MS/MS | LC/MS/MS    |
| LLOQ                             |          |             |
| Linear range                     |          |             |
| QC samples                       |          |             |
| Inter-day accuracy and precision |          |             |
| Intra-day accuracy and precision |          |             |
| Freeze-thaw stability            |          |             |
| Benchtop Stability at RT         |          |             |
| Long term at -70° C              |          |             |

|                                |  |  |
|--------------------------------|--|--|
| Recovery<br>Low<br>Med<br>High |  |  |
|--------------------------------|--|--|

If several different analytical methods were used, the difference in method and the LLOQs should be given, for example in a Table

| Analyte | Method | Assay Sensitivity ng/ml |
|---------|--------|-------------------------|
| 340     | LC/MS  | X                       |
| 344     | LC/MS  | Y                       |

Assay cross validation results should also be provided.

In this section in Tabular format also provide the assay performance from each study (QC data).

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** July 21, 2005  
**Application:** IND 53,950 ; Retigabine  
**Indication:** Epilepsy  
**Type of Meeting:** Telecon  
**Meeting Chair:** John Feeney, III, MD  
**Meeting Recorder:** Courtney Calder, Pharm.D.

### **FDA Attendees:**

John Feeney III, M.D., Team Leader  
Norman Hershkowitz, M.D., Medical Officer  
Ohidul Siddiqui, Ph.D., Biometrics  
Courtney Calder, Pharm.D., Project Manager

### **Sponsor Attendees:**

Kim Lamon, M.D., Ph.D. President and Chief Scientific Officer,  
Valeant Research & Development  
Cynthia Letizia, M.P.H., R.A.C. Senior Director, Regulatory Affairs  
Anil Hiteshi, R.A.C. Associate Director, Regulatory Affairs  
Rene Braeckman, Ph.D. Vice President, Project Management and  
Clinical operations  
Yong Kim, Ph.D. Senior Director, Biometrics  
Wayne Alves, Ph.D. Retigabine Global Team Leader

(b) (4)

The Division sent a letter to the sponsor dated June 29, 2005, which included comments regarding the special protocol assessments dated May 13, 2005. The firm requested a teleconference to discuss the comments in the letter.

**Discussion Points:** Below are the clarifications that relate to the numbered items in the letter.

1. One of your proposed studies will have 2 fixed-dose groups (600 mg/day and 900 mg/day) and a placebo group. The second proposed study will have a 1200 mg/day group and a placebo group. Viewed together, the results of these 2 studies will not tell us whether the 1200 mg/day group provides any additional benefit over the 900 mg/day group. We know you have a prior fixed-dose study that included both the 900 mg/day and 1200 mg/day doses, but we have not reviewed those results in detail and cannot speak to the strength of evidence that 1200 mg/day performs better than 900 mg/day. Therefore, unless you think there was a clear separation between 900 mg/day and 1200 mg/day in your previous study, you may wish to consider including a 900 mg/day, along with the planned 1200 mg/day dose group in your second planned study.

The Division clarified that the issues raised in question 1 are not related to approvability, but are issues of labeling.

**2. We have not completed the biopharm review of your proposed protocols. Therefore, comments about the biopharm sections of your protocols will be sent later.**

The Sponsor wanted assurance that pending biopharm comments will not require a change to the protocol. The division could not guarantee this.

**3. There is no need for co-primary endpoint analysis. You may define separate primary endpoints for the two different regulatory agencies (FDA and EMEA). We would recommend, for the FDA submission, that you utilize a single endpoint analysis based upon the percent change in seizure frequency.**

The division notes that separate outcomes for the FDA and the European community would be acceptable. Information for separate primary outcomes can be specified in the same protocol. For the FDA, the responder rate may be made a secondary outcome. There is precedent for this in other drug applications. The Sponsor agreed to this.

**4. We recommend that, as part of the *primary* analysis, you use a stepdown plan in your first study, examining the effects of 900 mg/day then 600 mg/day.**

The Sponsor agreed with a step-down analysis.

**5. We recommend that monitoring of kidney/bladder function should be increased in frequency. Thus, a urinalysis for both studies should be performed at the same frequency as the routine clinical laboratories. The AUA Symptom Index should be performed not only at baseline and last maintenance exam, but also at one or two additional times equally spaced during the treatment period. The post voiding residual ultrasound should not only be performed at baseline and 1 week into maintenance in the high dose study (Study 301), but also at an additional time point near the end of the study. Similar ultrasound evaluations should be performed for Study 302.**

The Sponsor agreed to expanding ultrasound monitoring, but noted that it cannot be expanded to all European sites as some are not equipped with this expertise. The Sponsor asked whether this was acceptable. The Division responded in the affirmative.

**6. As you have noted, there is an animal signal that retigabine may have some epileptogenic properties. To assist in examining this, you are analyzing responder rates for increases in seizures. In addition, we recommend that you analyze the incidence of new seizure types (e.g. incidence of status epilepticus, absence, myoclonic, new onset of secondary generalization, etc.) in patients without a history of these seizure types. Moreover an examination of changes in the frequency of seizure types, not meant to be treated by the drug, (e.g. myoclonic, absence, etc) may be helpful.**

The Sponsor agreed.

**7. An examination of bicarbonate should be added to as part of standard routine clinical laboratories**

The Sponsor agreed but noted that they question the reliability of the bicarbonate measures at some experimental sites.

**8. We told you at the end of phase 2 meeting that a separate, formal QT study may not be required if you included the elements of a formal QT study in your proposed phase 3 trials. EKGs performed at multiple timepoints after dosing represent a key element of a formal QT evaluation. While we understand from the aforementioned meeting that you intend to examine multiple time points, it is not clear in the present protocols as to how this will be accomplished. A formal study would usually require that multiple EKGs be obtained following a single dose during a given day at steady state. This design aspect does not appear to have been included in your protocols. Therefore, we would not consider these QT assessments adequate by today's standards. To strengthen the present proposed EKG studies, you should attempt to incorporate this and as many other aspects of the EKG study as described in the FDA draft guidance (<http://www.fda.gov/cder/guidance/6378dft.htm>). Moreover, a concentration and dose-response analysis may be helpful. It is also noted that while positive controls would also be helpful these agents may exacerbate seizures and are therefore not recommended. This, however, underscores the usefulness of a formal study in normal patients.**

The Sponsor notes that they included the requested information in the submission as an addendum to the protocol. The Division noted that this was not reviewed but will now be reviewed. The Division will get back to the Sponsor on this issue.

**9. You have not submitted the final statistical analysis plan. We will need to review this later.**

The Sponsor wished to relay that there will be no interim analysis. Statistics agreed. Otherwise all agreed to this item.

Minutes Preparer: \_\_\_\_\_  
Courtney Calder, Pharm.D.

Chair Concurrence: \_\_\_\_\_  
John Feeney III, MD

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John Feeney  
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 53,950

Valeant Pharmaceuticals International  
Attn: William L. Schary, Ph.D., R.A.C.  
Vice President, Regulatory Affairs  
3300 Hyland Ave  
Costa Mesa, CA 92626

Dear Dr. Schary:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Retigabine.

We also refer to your May 13, 2005, requests, serial number 164 and 165, for special clinical protocol assessments, received May 16, 2005. The protocols are entitled A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Retigabine (1200 mg/day) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures and A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Two Doses of Retigabine (900 mg/day and 600 mg/day) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures.

We have completed our review of your submission and, based on the information submitted, have the following comments.

1. One of your proposed studies will have 2 fixed-dose groups (600 mg/day and 900 mg/day) and a placebo group. The second proposed study will have a 1200 mg/day group and a placebo group. Viewed together, the results of these 2 studies will not tell us whether the 1200 mg/day group provides any additional benefit over the 900 mg/day group. We know you have a prior fixed-dose study that included both the 900 mg/day and 1200 mg/day doses, but we have not reviewed those results in detail and cannot speak to the strength of evidence that 1200 mg/day performs better than 900 mg/day. Therefore, unless you think there was a clear separation between 900 mg/day and 1200 mg/day in your previous study, you may wish to consider including a 900 mg/day, along with the planned 1200 mg/day dose group in your second planned study.
2. We have not completed the biopharm review of your proposed protocols. Therefore, comments about the biopharm sections of your protocols will be sent later.
3. There is no need for co-primary endpoint analysis. You may define separate primary endpoints for the two different regulatory agencies (FDA and EMEA). We would recommend,

for the FDA submission, that you utilize a single endpoint analysis based upon the percent change in seizure frequency.

4. We recommend that, as part of the *primary* analysis, you use a stepdown plan in your first study, examining the effects of 900 mg/day then 600 mg/day.

5. We recommend that monitoring of kidney/bladder function should be increased in frequency. Thus, a urinalysis for both studies should be performed at the same frequency as the routine clinical laboratories. The AUA Symptom Index should be performed not only at baseline and last maintenance exam, but also at one or two additional times equally spaced during the treatment period. The post voiding residual ultrasound should not only be performed at baseline and 1 week into maintenance in the high dose study (Study 301), but also at an additional time point near the end of the study. Similar ultrasound evaluations should be performed for Study 302.

6. As you have noted, there is an animal signal that retigabine may have some epileptogenic properties. To assist in examining this, you are analyzing responder rates for increases in seizures. In addition, we recommend that you analyze the incidence of new seizure types (e.g. incidence of status epilepticus, absence, myoclonic, new onset of secondary generalization, etc.) in patients without a history of these seizure types. Moreover an examination of changes in the frequency of seizure types, not meant to be treated by the drug, (e.g. myoclonic, absence, etc) may be helpful.

7. An examination of bicarbonate should be added to as part of standard routine clinical laboratories

8. We told you at the end of phase 2 meeting that a separate, formal QT study may not be required if you included the elements of a formal QT study in your proposed phase 3 trials. EKGs performed at multiple timepoints after dosing represent a key element of a formal QT evaluation. While we understand from the aforementioned meeting that you intend to examine multiple time points, it is not clear in the present protocols as to how this will be accomplished. A formal study would usually require that multiple EKGs be obtained following a single dose during a given day at steady state. This design aspect does not appear to have been included in your protocols. Therefore, we would not consider these QT assessments adequate by today's standards. To strengthen the present proposed EKG studies, you should attempt to incorporate this and as many other aspects of the EKG study as described in the FDA draft guidance (<http://www.fda.gov/cder/guidance/6378dft.htm>). Moreover, a concentration and dose-response analysis may be helpful. It is also noted that while positive controls would also be helpful these agents may exacerbate seizures and are therefore not recommended. This, however, underscores the usefulness of a formal study in normal patients.

9. You have not submitted the final statistical analysis plan. We will need to review this later.

If you have any questions, call Courtney Calder, Project Manager, at 301-594-5528.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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John Feeney  
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for Russell Katz, M.D.

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** November 2, 2004  
**Application:** IND 53,950; Retigabine  
**Indication:** Epilepsy  
**Type of Meeting:** EOP2  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Melina Griffis, R.Ph.

### FDA Attendees:

|                                           |                                        |
|-------------------------------------------|----------------------------------------|
| Russell Katz, M.D., Division Director     | John Feeney, M.D., Team Leader         |
| Norman Hershkowitz, M.D., Medical Officer | Sharon Yan, Ph.D., Biometrics          |
| Ed Fisher, Ph.D., Pharm/Tox               | Lois Freed, Ph.D., Pharm/Tox           |
| Kofi Kumi, Ph.D., Biopharm                | Melina Griffis, R.Ph., Project Manager |

### Sponsor Attendees:

|                         |                                |
|-------------------------|--------------------------------|
| Wayne Alves, Ph.D.      | Virinder Nohria, M.D., Ph.D.   |
| Karin Kook, Ph.D.       | John Dillberger, D.V.M., Ph.D. |
| Jacqueline French, M.D. | Cynthia McCormack, M.D.        |
| Roger Porter, M.D.      | Jane Fisher                    |

### Discussion Points: Below are the sponsor's questions with the appropriate FDA responses.

1. In humans, RGB is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes. RGB is excreted in urine as the parent drug or as the glucuronide of the parent or the pharmacologically active N-acetyl metabolite (AWD21-360). In rats, all major human metabolites are present in ratios similar to those in man. In dogs, the N-acetyl metabolite is absent. A preliminary study of AWD21-360 in dogs indicated the tolerability of the metabolite is greater than that of RGB. Xcel proposes a 4-week study of the N-acetyl metabolite (AWD21-360) in dogs. Does the Agency agree with this plan? **The proposed bridging study is acceptable; however, the duration of this study should be at least 3 months. Additional requirements may be needed if these studies show any findings of concern.**
2. Does the Agency agree that the completed and proposed nonclinical studies program (pharmacology, safety pharmacology, and toxicology) is adequate to support the ultimate registration of RGB? **The rat and rabbit embryo/fetal development studies (segment II) were not conducted at adequately high doses based on the lack of any maternal toxicity findings.**
3. The inherent pharmacokinetics of Retigabine have been characterized with the exception of the profile in special populations (subjects with renal and hepatic impairment and the elderly). Are the two special population studies and the population pharmacokinetic approach proposed adequate to support the ultimate registration of RGB? **In addition to the studies completed and the planned studies in renal and hepatic impaired**

patients, it is recommended the sponsor evaluate whether there are differences in pharmacokinetics due to ethnicity. It may be useful to evaluate the effect of genotype in this respect in the Phase III studies to explain any variability in exposure, efficacy or safety. Specifically, it may be useful to genotype for UDPGT (UGT1A1, to include \*28 in Caucasians and \*6 in Asians) and NAT. It is recommended that the sponsor refer to the guidance on renal and hepatic impairment in the design for the studies for these special populations. It is suggested that the sponsor provide for review and comments their plans for population pharmacokinetic, exposure-response (efficacy and safety including QT) study design and/or analyses in the phase III studies to the agency (OCPB). It is suggested the sponsor submit the plan prior to beginning the Phase III studies. The sponsor has conducted a food effect study on a 200 mg strength of Retigabine. It is recommended the sponsor conduct a food effect study on the highest strength they intend to market. The sponsor should thoroughly characterize the effect of Retigabine on QT. The sponsor is referred to the QT guidance on the FDA Website. It was noted that it is unlikely that healthy volunteers could tolerate a high enough dose to adequately study effects on QT. In addition, it was noted that moxifloxacin should be used with caution in patients with seizure disorders. The Sponsor plans to evaluate QT effect with a subset of patients in Phase III studies with intensive monitoring.

4. A number of drug-drug interactions studies investigating the effect of other AEDs on steady state of RGB and vice versa have been completed and no clinically important interactions were found. These have included carbamazepine, phenytoin, lamotrigine, valproate, topiramate and phenobarbital. Furthermore, RGB has low protein binding and is not metabolized by the CYP 450 system of enzymes. In the proposed Phase III studies, the effect of other AEDs on steady state PK of RGB will be further investigated using population PK modeling. Does the agency agree that the completed and proposed approach to evaluate interactions between RGB and commonly used AEDs are sufficient to address the potential for meaningful drug interactions? **Yes. However, Population Pharmacokinetic analysis alone cannot be used to definitively conclude whether or not there is an interaction between RGB and any concomitant medication. If a signal for interaction is seen in the population PK studies, then an in vivo study may be needed in addition to Population Pharmacokinetic analysis to quantify the magnitude of the effect. It is suggested that the sponsor submit their Population Pharmacokinetic design and analysis plan for review and comments prior to initiating the Phase III study. In addition, it is recommended that the Sponsor adequately assess the potential for induction of P450s. At the Sponsor meeting, it was recommended that in vitro induction studies be performed to include CYP1A2. (The Sponsor believes that in vivo studies have ruled out induction of CYP3A). Please refer to FDA guidance on In Vivo Drug Metabolism/Drug Interaction Studies and Population Pharmacokinetics.**
5. Does the Agency agree that the designs of the two proposed Phase III studies are adequate to support a claim for efficacy and safety of RGB as adjunctive therapy for treatment of partial onset seizures with and without secondary generalization in adults

with epilepsy? **The primary outcome is the change in total partial seizure frequency per twenty-eight days from the baseline to the double blind period converted into an RRatio. The RRatio should not be used as it is the division's experience that although the goal is to normalize the data, this is not accomplished. Moreover, the measure is somewhat obscure and difficult to interpret clinically. A more traditional measure should be used such as simple frequency or log transformed frequency. Presently one phase III study is examining 900 and 1200 mg doses and the other is examining only the 1200 mg dose. With regard to the latter study the division recommended that it may be better to obtain more dose response data ; i.e. examine both 600 mg and 900mg in addition to 1200 mg.**

6. Does the Agency agree that the design of Study 3065A1-205 (summarized in Section 6; full report submitted in Serial No. 148, dated 19 December 2003) meets the requirements of an adequate and well-controlled clinical trial of the safety and efficacy of RGB as adjunctive therapy for treatment of partial onset seizures in adults? **Yes**
7. Xcel intends to comply with 21 CFR 314.55, which requires assessment of safety and efficacy in the relevant pediatric subpopulation. Because of the novel mechanism of action of RGB, we believe that the start of pediatric pharmacokinetic, efficacy, and safety studies should be deferred until after the completion of the Phase III studies in adults. Since the results from these pediatric studies will not be available at the time of original submission of the marketing application for RGB as an adjunctive treatment for partial onset seizures in adults with epilepsy, we request that submission of the pediatric data in the original submission be deferred. Does the Agency concur with this approach? **We concur with the approach.**
8. RGB has been administered to approximately 900 human subjects, of which approximately 575 are subjects with epilepsy and 330 are healthy volunteers. RGB has been administered as an adjunctive therapy to approximately 575 epileptic subjects, with nearly 250 subjects receiving RGB for 6 months, 150 subjects for 1 year, and 50 for 2 years. The proposed Phase III clinical development program will include an additional 550 subjects with epilepsy exposed to RGB, bringing the total RGB exposure within the recommendations of ICH guidelines. At the completion of the Phase III program, it is anticipated that a total of 1564 human subjects (healthy volunteers and subjects with epilepsy) will have received at least one dose of RGB. Of these, 1114 will have been subjects with epilepsy. Of these, more than 600 subjects with epilepsy will have been exposed to RGB for a minimum of 6 months and 300 subjects for a minimum of 12 months. Does the Agency agree that the completed studies thus far and the proposed studies will provide sufficient human exposure for an adequate evaluation of safety at the time of submission? **The completed and proposed study should jointly result in adequate patient number and exposure.**
9. RGB is a potassium channel opener (enhancer). Since potassium plays an important role in cardiac action potential conduction, the effect of RGB on cardiac tissue has been extensively evaluated with no apparent effects noted in numerous in vitro and in vivo models. At therapeutically relevant concentrations, RGB has been shown to have no

effect on cat ventricular myocytes, dog purkinje fibers, guinea-pig cardiac impulse generation, or other cardiovascular parameters in anesthetized or conscious dogs or pigs. The effect of RGB on hERG channels has also been investigated, and concentrations of 100 micromolars were needed to have an appreciable effect in this test system. In Phase I and Phase II studies, ECG and Holter monitor data have been collected and analyzed; and no clinically important effect on QTc has been found. In the Phase III studies, ECGs will be collected for an estimated 550 subjects at each visit during the double-blind treatment period. The ECGs will be obtained at varying times after dose administration, along with concomitant plasma levels of RGB. Using a population pharmacokinetic approach, a correlation between plasma levels and QTc will be evaluated. Does the Agency agree that, collectively, these studies are sufficient to assess the cardiovascular safety of RGB? **The division noted that it was unclear as to the specifics of the degree and quality of the data presently available. The Sponsor noted that while there are no examinations using repeated measurements for individual time points there is data on EKGs during steady state at Tmax. The Sponsor noted that they intended to build an EKG trial into the present phase III studies. The division noted this may suffice. The Sponsor should build into this trial experimental design elements used in routine QT studies such as multiple time points (over approximately 24 hours), averaging of repeated measures at each time point (e.g. 3), drug/placebo etc. The use of a positive control was also discussed; however the Sponsor expressed safety concern for the use of such agents in epileptic individuals.**

#### Other Issues:

- The division raised concern regarding bladder toxicity identified in animals and asked for more information regarding the pathological process. The Sponsor noted that it may be a result of the confluence of two processes: the suppression of bladder function and the precipitation of possibly toxic crystal metabolites. The division requested that bladder issues be carefully monitored. This would include adding safety monitoring to the protocols using: American Urological Association Symptom Index, more frequent chemical and microscopic UA (i.e. these should be performed at every safety follow up), non-invasive monitoring of bladder dynamics through post voiding sonographic bladder residuals, and consultation with urology during the study.
- It was also noted that no serious adverse events associated with bilirubin elevation was identified in reported serious adverse events and that no “clinically significant bilirubin elevation was identified.” However, some adverse events were associated with elevations in bilirubin. Presumably this means that bilirubin was no greater than 1.5X above normal elevated. The Sponsor was asked to review these latter events to ascertain that they do not represent episodes of hepatic toxicity.
- Animal studies indicate that Retigabine is potentially epileptogenic. Because of this the division is very interested in identifying any evidence of a potential convulsive effect in clinical studies. Among the analyses that should be performed are the examination for new seizure types and the incidence of status epilepticus following treatment.

Minutes Preparer: \_\_\_\_\_  
Melina Griffis R.Ph.

Chair Concurrence: \_\_\_\_\_  
Russell Katz, M.D.

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Russell Katz

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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** October 7, 2004  
**Application:** IND 53,950;Retigabine  
**Indication:** Epilepsy  
**Type of Meeting:** EOP2/CMC only  
**Meeting Chair:** Maryla Guzewska, Ph.D.  
**Meeting Recorder:** Melina Griffis, R.Ph.

### FDA Attendees:

Maryla Guzewska, Ph.D. Janusz Rzeszotarski, Ph.D.  
Melina Griffis, R.Ph., Project Manager

### Sponsor Attendees:

Wayne Alves, Ph.D. Karin Kook, Ph.D.  
Virinder Nohra, M.D., Ph.D. Sally Look, Ph.D.  
John Bettis, Ph. D. Richard Rodebaugh, Ph.D.  
Susan Skinner Mario Weingart  
Torsten Hoffmann Sabin Rothmann  
Jill Kompa

**Discussion Points: Below are the sponsor's questions with the appropriate FDA responses.**

### Drug Substance

1. Does the Agency agree that [REDACTED] (b) (4) qualify as starting materials for the drug substance synthetic process? Does the Agency agree with the approach for release testing of each of the proposed starting materials (stated tests and specifications) for retigabine? Reference Sections 3.2.S.2.2 and 3.2.S.2.3 of the briefing document. **Yes**
2. Does the Agency agree to the approach for release and stability testing of the drug substance as provided in the specifications for retigabine? *Reference Section 3.2.S.4, Table 3 of the briefing document.* **Yes**
3. Does the Agency agree that the drug substance stability protocol outlined for the registration stability lots is satisfactory to support NDA submission? *Reference Section 3.2.S.7, Table 8 of the briefing document.* **Yes. The sponsor stated that 3 NDA drug substance stability batches will be produced with the plan to make 3 drug product batches if possible, otherwise 2 would be available.**
4. The site of drug substance manufacture for lots of retigabine used in production of Phase 3 clinical supplies will change from [REDACTED] (b) (4) to a new site, probably another [REDACTED] (b) (4) site. The new site will also be the intended commercial site of retigabine [REDACTED] (b) (4). After process transfer, three NDA registration stability lots of drug substance will

be manufactured at the new production site. Does the Agency agree with the regulatory and development strategy supporting the site transfer described in the briefing document?

*Reference the Introduction and Section 3.2.S.2.1 of the briefing document. Yes. There are 3 polymorphic forms of the drug substance, the sponsor confirmed that they would only proceed with the polymorph* (b) (4)

#### Drug Product

5.

(b) (4)

6. Does the Agency agree that the drug product stability protocol outlined for registration stability lots to be manufactured at the intended commercial manufacturing site is satisfactory to support NDA submission? Is the proposed bracketing approach of placing samples for three batches each of the 50 and 400 mg tablets on stability and only one batch each of 100 and 300 mg tablets acceptable to cover the 200 mg tablet strength, noting that if the 200 mg tablets are proposed for marketing, stability data will not be included in the NDA for this strength? *Reference Section 3.2.P.8, Table 19 and the following text of the briefing document. Yes*
7. Phase 3 clinical studies will be initiated with Retigabine film-coated tablet supplies manufactured at (b) (4) the site used to manufacture Phase 2 clinical trial material. A new drug product manufacturing site will be selected for the completion of Phase 3 clinical studies and future commercialization. Does the Agency agree to the regulatory and development strategy for bridging Chemistry, Manufacturing, and Controls (CMC) data generated on Retigabine film-coated tablets initially used in Phase 3 clinical batches to the new manufacturer that will provide the remainder of Phase 3 clinical supplies and future commercial product? Specifically, does the Agency agree to the plan to generate comparative analytical batch analysis data, including dissolution data, and long-term stability data for samples of batches manufactured at the intended commercial production site to support the new manufacturing site? *Reference the Introduction to the briefing document Yes, The sponsor stated that Phase III manufacturing would be initiated at the (b) (4) site and then switched once an alternative site is located. At the time of NDA submission 12 month of stability and 6 months of accelerated stability will be provided.*
8. Phase 3 and primary NDA registration stability batches of drug product will not be printed; however, the intended commercial tablets will be printed for product identification. The current plan is to verify that there is no analytical interference from the ink; also, comparative dissolution data will be generated to compare printed and unprinted tablets. In addition, ICH photostability studies using printed tablets for NDA filing will be performed. ICH stability studies using three printed process validation batches manufactured after NDA filing will also be conducted and the data will be submitted in the annual report. Is this

approach acceptable to the Agency? *Reference Sections 3.2.P.5 and 3.2.P.8 of the briefing document.* **Yes**

Minutes Preparer: \_\_\_\_\_  
Melina Griffis R.Ph.

Chair Concurrence: \_\_\_\_\_  
Maryla Guzewska, Ph.D.

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Maryla Guzewska  
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