CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022345Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK REMS MODIFICATION FINAL REVIEW

Date:	June 10, 2011
To:	Russell Katz, M.D., Director Review Division of Neurology Products (DNP)
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead,** Risk Management Analyst (RMA) Reema Jain, Pharm.D., M.P.H., DRISK **Team Leader,** Kendra Worthy, Pharm.D., DRISK
DRISK Review Team:	Mary Dempsey, Risk Management Program Coordinator, DRISK Jodi Duckhorn, M.A., Senior Social Science Reviewer Kate Heinrich, M.A., Health Education Reviewer, DRISK Laurie Kelley, Safety Regulatory Project Manager, OSE Anahita Tavakoli, MA, Health Education Reviewer
Subject:	REMS Final Review
Drug Name (Established Name):	Potiga™ (ezogabine)
Application Type/Number:	NDA 22-345
Applicant:	Valeant Pharmaceuticals North America
OSE RCM #:	2010-1284

1. INTRODUCTION

This is the Division of Risk Management's (DRISK) review of the proposed REMS for Potiga™ (ezogabine), submitted by the sponsor on August 26, 2010 and June 6, 2011 in response to FDA's notification letter dated August 16, 2010. The sponsor's proposed REMS includes a Medication Guide and Communication Plan to mitigate the risks of urinary retention and suicidality associated with the administration of Potiga. The FDA subsequently determined that the Medication Guide was not a required element of the REMS.

2. MATERIALS REVIEWED

The following materials were reviewed:

- Valeant Pharmaceuticals North America proposed REMS for Potiga™ (ezogabine) tablets, including communication plan materials, submitted August 26, 2010, June 6, 2011, and June 9, 2011.
- Valeant Pharmaceuticals North America proposed REMS supporting document submission for Potiga™ (ezogabine) tablets submitted August 26, 2010, June 6, 2011, and June 9, 2011.

The following materials were referenced in this review:

Prescribing information

- Valeant Pharmaceuticals North America proposed Prescribing Information (PI) for Potiga™ (ezogabine) tablets, July 26, 2010

FDA Reviews and Correspondence

- FDA REMS Element Retraction Letter to Valeant Pharmaceuticals, signed March 25, 2011
- Potiga™ (ezogabine) tablets, DRISK Review of Patient Labeling (Medication Guide), dated October 13, 2010
- FDA Review Extension- Major Amendment Letter dated August 30, 2011
- FDA Pre-Approval REMS Notification Letter to Valeant Pharmaceuticals North America, signed August 16, 2010
- FDA REMS Memorandum for Potiga™ (ezogabine) tablets, August 13, 2010
- Potiga™ (ezogabine) tablets, FDA/CDER Peripheral and CNS Drugs Advisory Committee Meeting Background Package, dated August 11, 2010
- Potiga™ (ezogabine) tablets, DRUP Review, dated June 09, 2010

3. BACKGROUND

Valeant Pharmaceuticals North America (Valeant) submitted a new drug application (NDA 22-345) for Potiga™ (ezogabine) tablets, an antiepileptic drug (AED), on October 30, 2009, with the proposed indication for adjunctive therapy in the treatment of partial-

onset seizures with or without secondary generalization in patients with epilepsy, aged 18 years or older. The application included the submission of a Medication Guide to address the risk of suicidal thoughts and behavior associated with the class of AEDs and the risk of urinary retention associated with Potiga.

On August 11, 2010, a Peripheral and Central Nervous System Drugs Advisory Committee meeting was held to discuss the benefit-risk profile of Potiga. Although DRISK was not included in the post-AC discussion on the need to have additional measures within the REMS, the Agency sent the sponsor a Pre-Approval REMS Notification letter, dated August 16, 2010, as a result of the discussions and recommendations at the advisory committee meeting. Specifically, the Agency determined that a REMS is necessary for Potiga to ensure the benefits outweigh the risks of (b) (4) urinary retention associated with Potiga and its associated morbidities. The letter indicated that the REMS should include a Medication Guide and communication plan. Valeant submitted a proposed REMS on August 26, 2010. The application submitted on April 15, 2011 referenced the proposed REMS submitted on August 26, 2010. The submission of the REMS triggered a major amendment, which extended the user fee goal date three months to November 30, 2010.

Subsequently, on November 30, 2010, the Agency issued a Complete Response letter to Valeant due to (1) unacceptable levels of mutagenic impurities; and (2) lack (b) (4) On April 15, 2011, Valeant resubmitted the application as a Class 1 response to the November 30, 2010 action letter. The user fee goal date is June 15, 2011.

The Agency issued a REMS Element Retraction letter on March 25, 2011 that addressed removing the MG from the REMS based on the Draft Guidance for Industry titled Medication Guides-Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS). The Agency has the authority to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS, and may decide the Medication Guide should be required as labeling but not part of a REMS. The decision to remove MG from the class AED REMS was a joint decision between DNP and DRISK.

4. RESULTS OF REVIEW OF PROPOSED REMS

4.1. Goals

The goal of the REMS for Potiga is to inform healthcare professionals of the risk of urinary retention and the symptoms of acute urinary retention in patients taking POTIGA.

4.2. REMS Elements

4.2.1. Communication Plan

A communication plan will be implemented to healthcare professionals to support the implementation of this REMS and includes the following elements:

1. A Dear Healthcare Professional (HCP) Letter designed to disseminate information about the risk of urinary retention with POTIGA. Within the first four weeks of retail availability of POTIGA, and annually for the next two years, the Dear Healthcare Professional (HCP) letters will be mailed to the following audiences:
   a. Prescribing physicians (i.e., Epileptologists, Neurologists and Neurosurgeons) and physicians who may evaluate and treat patients with possible urinary retention (i.e., Urologists and Emergency Room Physicians)
   b. Pharmacists dispensing POTIGA tablets and the Medication Guide

   After the initial mailing, new prescribers of POTIGA will be included in subsequent mailings of the Dear HCP letter.

   The mailing will include a copy of the Prescribing Information (PI) and the Medication Guide.

2. REMS Program Website
   a. The REMS Program website for HCPs will be accessed directly from the homepage for POTIGA. This REMS Program information will be shown automatically, such that HCPs visiting the healthcare provider area of the website can view the REMS Program information prior to viewing other areas of the website. Included in the information will be a brief explanation of a REMS, the goal of the REMS for POTIGA, and separate links for downloadable versions of the full Prescribing Information, the Medication Guide, and the Dear HCP Letters. The webpage also includes the indication for POTIGA and Important Safety Information for Healthcare Professionals. Also on the page is a link for patient and caregivers to return to the POTIGA homepage.
   b. The online information will be available to all healthcare professionals as it is in the public domain.

4.2.2. REMS Assessment

The Sponsor will submit assessments of the REMS to FDA annually for the first 3 years and 7 years from the date of initial approval of the REMS.

The following information needed for assessments is included in the REMS supporting document:

a. Assessment of health care professionals who will communicate with patients at the time of prescribing or dispensing POTIGA:

   i. A survey will be conducted among a sample of prescribing physicians to evaluate whether they can recall the risk of urinary retention with POTIGA

   ii. A survey to evaluate where HCPs prefer to seek information for POTIGA, for example Dear HCP letters, website, or product labeling.

   iii. A survey of pharmacists to evaluate whether they can recall the risk of urinary retention with POTIGA.

5. DISCUSSION AND CONCLUSION

The sponsor's proposed changes to the REMS in their June 9, 2011 submission are acceptable; DRISK recommends the REMS for approval.

6. ATTACHMENTS

- APPENDIX A: REMS
- APPENDIX B: Dear Healthcare Professional Letter – Physicians
- APPENDIX C: Dear Healthcare Professional Letter – Pharmacist

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/s/

KENDRA C WORTHY
06/10/2011

MARY E WILLY
06/10/2011
I concur; signing for Claudia Karwoski

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Compliance

REMS Memorandum

TO: NDA 22-345

THROUGH: Suzanne Barone, Ph. D., Team Leader
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance

FROM: Kendra Biddick, CSO
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance

SUBJECT: Office of Compliance review and comment on the adequacy of the proposed risk evaluation and mitigation strategy (REMS) for Potiga (ezogabine)

This memo is the Office of Compliance response to the proposed Medication Guide and Communication Plan only REMS for Potiga (ezogabine) submitted by Valeant Pharmaceuticals on August 26, 2010.

Background

In 2007, the Food and Drug Administration Amendments Act (FDAAA) granted the FDA authority to require risk evaluation and mitigation strategies (REMS) to help ensure that the benefits of a drug outweigh the risks. FDAAA also gave the FDA additional enforcement tools including misbranding charges and civil penalties for sponsors that do not follow requirements of an approved REMS.

The goals of the proposed REMS are:

1. To inform healthcare professionals and patients of the risk of urinary retention with POTIGA (b) (4)
.
(b) (4)

The proposed REMS includes a medication guide, communication plan, and a timetable for submission of assessments.

OC Observations

Medication Guide

OSE and OND have determined that a Medication Guide is not required as part of this proposed REMS. It should be removed from the draft REMS and the other appended documents should be renumbered accordingly.

Communication Plan

The Communication Plan includes three different versions of a Dear Healthcare Professional (DHCP) letter to be distributed "within the first four weeks of retail availability of the Potiga and annually for the next two years". The DHCP letters will be addressed to prescribing physicians (epileptologists, neurologists, and neurosurgeons) to physicians who may evaluate and treat patients with possible urinary retention, (urologists and emergency room physicians), and to pharmacists. Each mailing will also include a copy of the prescribing information (PI) and the medication Guide. Valeant also proposes a Potiga website with a REMS-dedicated landing page.

Timetable for Submission of Assessments

The timetable for submission of assessments language is acceptable. We defer to OND/OSE on the frequency of assessments.

REMS Assessment Plan

The REMS assessment plan includes assessment of the Medication Guide and the knowledge prescribers and pharmacists retain as a result of the communication plan. It does not include assessment of the implementation of the communication plan by Valeant.

OC Recommendations to OND/OSE.

The start date of the Communication Plan should be amended to start at a date relative to the approval date of the REMS, for instance; within 60 days of the date the REMS is approved.

The Information Required for Assessments section of the approval letter should include the following for the Communication Plan;

a. Date of retail availability of Potiga.
b. Sources of lists of prescriber and pharmacist addresses
c. Date(s) of distribution
d. Method of distribution (e.g., mail, email, contract carrier, etc.)
e. Number of recipients on each distribution list
f. Number of documents returned (undelivered)

g. List of all documents included in each distribution.

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/s/

KENDRA A BIDDICK
06/01/2011

SUZANNE BARONE
06/01/2011

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK INTERIM REMS REVIEW

Date:	May 31, 2011
To:	Russell Katz, MD, Director Division of Neurology Products (DNP)
Through:	Claudia Karwoski, PharmD, Director Division of Risk Management (DRISK)
From:	**Scientific Lead,** Risk Management Analyst (RMA) Reema Jain, PharmD, MPH, DRISK **Team Leader,** Kendra Worthy, PharmD, DRISK
DRISK Review Team:	Mary Dempsey, Risk Management Program Coordinator Kate Heinrich, M.A., Health Education Reviewer Anahita Tavakoli, MA, Health Education Reviewer Jodi Duckhorn, M.A., Senior Social Science Reviewer
Subject:	Interim REMS Review **Comments Set # 1**
Drug Name (Established Name):	Potiga™ (ezogabine)
Therapeutic Class:	Anticonvulsant
Dosage and Route:	Oral tablets
Application Type/Number:	NDA 22-345
Applicant:	Valeant Pharmaceuticals North America
OSE RCM #:	2011-1284

1. INTRODUCTION

The purpose of this interim review is to provide recommendations and seek clarification on the applicant's proposed POTIGA REMS submitted on August 26, 2010. The review includes recommendations to the review division and letter-ready comments for the applicant.

This review addresses the REMS document, Dear Healthcare Provider (DHCP) Letter, Dear Pharmacist Letter, and REMS website.

2. MATERIALS REVIEWED

The following materials were reviewed by DRISK for comment in this interim review:

- Valeant Pharmaceuticals North America proposed REMS for Potiga™ (ezogabine) tablets, including communication plan materials, submitted August 26, 2010.
- Valeant Pharmaceuticals North America proposed REMS supporting document submission for Potiga™ (ezogabine) tablets submitted August 26, 2010.

The following materials were referenced in this interim review:

Prescribing information

- Valeant Pharmaceuticals North America proposed Prescribing Information (PI) for Potiga™ (ezogabine) tablets, July 26, 2010Sponsor Submissions

FDA Reviews

- Potiga™ (ezogabine) tablets, DRISK Review of Patient Labeling (Medication Guide), dated October 13, 2010
- FDA Pre-Approval REMS Notification Letter to Valeant Pharmaceuticals North America, signed August 16, 2010.
- FDA REMS Memorandum for Potiga™ (ezogabine) tablets, August 13, 2010
- Potiga™ (ezogabine) tablets, FDA/CDER Peripheral and CNS Drugs Advisory Committee Meeting Background Package, dated August 11, 2010
- Potiga™ (ezogabine) tablets, DRUP Review, dated June 09, 2010Document xx

3. BACKGROUND

On October 30, 2009, Valeant Pharmaceuticals North America (Valeant) submitted a new drug application (NDA 22-345) for Potiga™ (ezogabine) tablets, an antiepileptic drug (AED), indicated for adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 18 years or older. The application included the submission of a Medication Guide to address the risk of suicidal thoughts and behavior associated with the class of AEDs and the risk of urinary retention associated with Potiga. Subsequently, on November 30, 2010, the Agency issued a Complete Response letter to Valeant due to (1) unacceptable levels of mutagenic impurities; and (2) (b) (4) On April 15, 2011, Valeant resubmitted the application as

a Class 1 response to the November 30, 2010 action letter. The user fee goal date is June 15, 2011.

4. REMS Summary

4.1. Required REMS

On August 11, 2010, a Peripheral and Central Nervous System Drugs Advisory Committee meeting was held to discuss the benefit-risk profile of Potiga. Although DRISK was not included in the post-AC discussion on the need to have additional measures within the REMS, the Agency sent the sponsor a Pre-Approval REMS Notification letter, dated August 16, 2010, as a result of the discussions and recommendations at the advisory committee meeting. Specifically, the Agency determined that a REMS is necessary for Potiga to ensure the benefits outweigh the risks of (b) (4) of urinary retention associated with Potiga and its associated morbidities. The letter indicated that the REMS should include a Medication Guide and communication plan. Valeant submitted a proposed REMS on August 26, 2010. The application submitted on April 15, 2011 referenced the proposed REMS submitted on August 26, 2010.

4.2. Applicant's Proposed REMS

The proposed REMS includes a Medication Guide and a communication plan. The goals of the REMS are as follows:

- To inform healthcare professionals and patients of the risk of urinary retention with POTIGA (b) (4)

A Medication Guide will be dispensed with each prescription. The communication plan includes three Dear Healthcare Professional (DHCP) Letters and a website. Each proposed DHCP letter will be provided to prescribing physicians (Epileptologists, Neurologists, and Neurosurgeons), physicians who may evaluate and treat patients with possible urinary retention (Urologists and emergency room physicians), and pharmacists.

5. RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Potiga (ezogabine) tablets REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the user fee goal date for this NDA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for Potiga. Appended to this review is the REMS proposal, DHCP Letter for prescribers, and DHCP Letter for pharmacists, including our track changes versions (see ATTACHMENT A, ATTACHMENT B, and ATTACHMENT C, respectively). The applicant should be reminded that the REMS Supporting Document and REMS materials (i.e., DHCP letter and REMS Program website) must be consistent with all changes made to the REMS document and to the labeling.

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

6. RECOMMENDATIONS FOR THE APPLICANT

6.1. REMS

See Appendices for tracked changes.

6.1.1. Goals

Revise the REMS goals as follows:

- (b) (4)

6.1.2. Medication Guide

We have determined that a Medication Guide is not required as part of your proposed REMS but will continue to be part of the approved labeling in accordance with 21 CFR part 208; therefore, we have removed the Medication Guide language (including patient surveys) from the REMS document/materials. Comments on your proposed Medication Guide will be provided separately.

6.1.3. Communication Plan

Revise the Communication Plan as follows:

1. A definite time period, including initiation date and end date, is needed in your communication plan for all communication activities. Currently you propose the DHCP letters to be sent out within 4 weeks of retail availability of Potiga, with no parameters for that date. We recommend sending the letter within a set timeframe, for example, within 60 days of approval of Potiga.
2. Valeant will send the communication plan materials to targeted providers within four weeks of retail availability and yearly for 2 years thereafter. Any new prescribers of Potiga should be included in the subsequent mailings of the DHCP letter. Revise the dissemination strategy to identify and reach new prescribers regardless of use or specialty for 2 years after product approval. These details should be included in the REMS and the REMS Supporting Document.
3. Provide details about the third-party databases from which the mailing list will be derived to justify that mailings are sent to a comprehensive listing of the target audience of HCPs currently or potentially treating epilepsy patients in the proposed communication plan.
4. Descriptions of the Potiga.com homepage, outside of the link to the REMS dedicated webpage, should be removed from the REMS document. Also remove Appendix E (Potiga.com homepage) from the REMS document.
5. DHCP Letter for Physicians: The DHCP Letter for neurologists, neurosurgeons, and epileptogists is very similar the DHCP Letter for urologists and emergency room

physicians. These letters can be combined so that distinct messages to each target separate audience are clear. See ATTACHMENT B for track changes.

6. DHCP Letter for Pharmacists: See ATTACHMENT C for track changes.
7. REMS Program Website:
   a. Replace the first paragraph on the REMS link with the following language:
      "A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks."
   b. The goals listed on the website must be consistent with the goals in the approved REMS.

6.1.4. Element to Assure Safe Use

Not applicable

6.1.5. Implementation System

Not applicable

6.1.6. Timetable for Submission of Assessments

The timetable for submission of assessments should be revised to annually for the first 3 years and 7 years from the date of initial approval of the REMS.

6.2. Supporting Document

1. Revise the REMS Supporting Document to be consistent with all changes made to the REMS document.
2. Revise the REMS Supporting Document to include a section titled: Information Needed for Assessments. Information needed for assessments should include, but may not be limited to, the following:
   a. A survey of prescribers' and pharmacists' understanding of the serious risks associated with Potiga and the symptoms of acute urinary retention
   b. A summary of reports of all potential or diagnosed cases of urinary retention
3. Remove the sections pertaining to the Medication Guide from the REMS Supporting Document (e.g., "3.1. Medication Guide" and "5.1. Assessment of the Medication Guide").

6.3. Information Needed for Assessment

6.3.1. Surveys

Submit for review the detailed plan you propose to use to evaluate prescribers' and pharmacists' understanding about the safe use of Potiga. You may submit the proposed plan after approval of the REMS; however, submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." Make sure the submission includes all methodology and

instruments used to evaluate the knowledge about the risks associated with and safe use of Potiga.

1. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, or on-line.

   Explain how often you perform non-respondent follow-up or reminders.

   If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

   Explain how you select recruitment sites.

   Submit for review any recruitment advertisements.

2. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
3. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
4. Ensure the sample is demographically representative of the population who prescribe (doctors) and dispense (pharmacies) the drug, regardless of the condition for which they use or prescribe it.
5. List the inclusion criteria for prescribers and pharmacies.

   Submit any screener instruments, and describe any quotas of sub-populations used.

6. Explain how you administer surveys and the intended frequency.

   Offer respondents multiple options for completing the survey. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

   Explain how you train surveyors.

7. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
8. Submit for review the introductory text used to inform respondents about the purpose of the survey.

   Tell potential respondents that their answers will not affect their ability to prescribe (doctors) or dispense (pharmacies) the drug and that their answers and personal information will be kept confidential and anonymous.

9. Clarify in your methodology that respondents are eligible for one wave of the survey only.
10. Analyze results on an item-by-item or variable-by-variable basis. You may present the date using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

    You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

Regarding an assessment of healthcare providers' knowledge:

11. The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating healthcare providers' knowledge of:
    - the serious risks associated with use of Potiga,
    - how to properly prescribe Potiga,
    - how to properly monitor for the serious risks associated with the use of Potiga;

    The assessment does not assess healthcare providers' comprehension of the educational materials.

    Do not offer respondents an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
13. Ensure the healthcare provider knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials.

    Ensure questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure each question has an "I don't know" answer option.

    Randomize the order of the multiple choice responses on each survey.

14. Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions.

    Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

    Explain if and when any education will be offered for incorrect responses.

15. Use the following (or similar) questions to assess receipt and use of the educational materials.
    - Prior to today, which of the following were you aware of or received with regard to Potiga? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	□	□
Medication Guide	□	□
Dear Healthcare Provider Letter	□	□
Something else - please explain:	□	□
None of the above	□	□

- Did you read the Full Prescribing Information?
  a) All,
  b) Most,
  c) Some,
  d) None
  e) I did not receive the Potiga Full Prescribing Information
- Did you read the Medication Guide?
  a) All,
  b) Most,
  c) Some,
  d) None
  e) I did not receive the Potiga Medication Guide
- Did you read the Dear Healthcare Provider Letter?
  a) All,
  b) Most,
  c) Some,
  d) None
  e) I did not receive the Potiga Dear Healthcare Provider Letter
  f) Do you have any questions about any of the educational materials related to Potiga? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

6.4. Post-Marketing Requirements

Not applicable.

6.5. Submission Instructions

1. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document. Provide a track changes and a clean version of all revised materials and documents.

2. Format Request:
   a. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.
   b. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.
   c. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document. However, changes must be noted using PDF mark-up tools.

7. ATTACHMENTS

- ATTACHMENT A: REMS
- ATTACHMENT B: Dear Healthcare Professional Letter – Physicians
- ATTACHMENT C: Dear Healthcare Professional Letter – Pharmacist

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/s/

REEMA JAIN
05/31/2011

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION 1
DIVISION OF NEUROLOGY PRODUCTS

NDA/BLA #s: 022345
Products: Potiga (ezogabine) Tablets
APPLICANT: Valeant Pharmaceuticals
FROM: Ellis Unger, M.D.
DATE: May 18, 2011

The purpose of this memorandum is to document the rationale for retracting the requirement for a Medication Guide to be an element of the risk evaluation and mitigation strategy (REMS) for Potiga (ezogabine) tablets. This requirement was stated in our REMS notification letter dated August 16, 2010. The REMS was required to ensure that the benefits of Potiga (ezogabine) tablets would outweigh the risks of (b) (4) urinary retention and its associated morbidities. Our rationale for requiring a REMS at that time was documented in a memorandum also dated August 16, 2010. The REMS was to include the following elements: a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. A proposed REMS including these elements was received on August 26, 2010.

The February 2011 Draft Guidance for Industry, which is entitled *Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS),* states that the FDA may approve a Medication Guide under 21 CFR 208 without requiring the Medication Guide to be a part of a REMS when the Medication Guide is adequate to address the serious and significant public health concern and meets the standard set forth under that regulation.

In light of this Draft Guidance, the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) have determined that the Medication Guide is no longer necessary as an element of the REMS for Potiga (ezogabine) tablets to ensure that the benefits of the drug outweigh the risks described above because the labeling will be adequate to address the serious and significant public health concern and will meet the standard in 21 CFR 208.1. The Medication Guide will be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

The elements of the REMS will be a communication plan and a timetable for submission of assessments of the REMS.

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/s/

KAREN D ABRAHAM-BURRELL
05/26/2011

ELLIS F UNGER
05/26/2011

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DEFER COMMENT MEMO

Date:	November 10, 2010
To:	Russell Katz, MD, Director Division of Neurology Products (DNP)
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead,** Risk Management Analyst (RMA) Reema Jain, Pharm.D., M.P.H., DRISK **Team Leader,** Kendra Worthy, Pharm.D. DRISK **DRISK Review Team** Mary Dempsey, Risk Management Program Coordinator, DRISK Kate Heinrich, M.A., Health Education Reviewer, DRISK Jodi Duckhorn, M.A., Senior Social Science Reviewer, DRISK Laurie Kelley, Safety Regulatory Project Manager, OSE
Subject:	Defer Comment on the proposed REMS for Potiga™ (ezogabine)
Drug Name (Established Name):	Potiga™ (ezogabine)
Application Type/Number:	NDA 22-345
Applicant/Sponsor:	Valeant Pharmaceuticals North America
OSE RCM #:	2009-2345

This memo is to defer comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) and communication plan materials for Potiga™ (ezogabine) tablets submitted with the New Drug Application (NDA) 22-345 for adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 18 years or older.

On August 16, 2010, the Agency notified the applicant of the requirement of a REMS consisting of a Medication Guide and communication plan to ensure that the benefits of the drug outweigh the increased risk of suicidal thoughts and behavior associated wtih the class of antiepileptic drugs (AEDs), of which Potiga™ (ezogabine) is a member, and the increased risk of urinary retention and its associated morbidities. The applicant submitted a proposed REMS August 26, 2010.

A Complete Response letter will be issued by the review division due to outstanding pharmacology deficiencies related to the potential for genotoxicity by an impurity found in the tablet. Therefore, DRISK defers comment on the sponsor's REMS proposal and communication plan at this time.

A final discussion on the appropriate risk management strategy will be undertaken after the sponsor submits a satisfactory response to the Complete Response letter.

Please send DRISK a new consult request at such time. This memo serves to close the existing consult request for Potiga™ (ezogabine) oral tablets under NDA 22-345.

Please notify DRISK if you have any questions.

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/s/

REEMA JAIN
11/10/2010

CLAUDIA B KARWOSKI
11/10/2010
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Neurology Products

NDA:	022345
Products:	Potiga (ezogabine) Tablets
APPLICANT:	Valeant Pharmaceuticals
FROM:	Ellis Unger, M.D. Deputy Director, Office of Drug Evaluation-I
DATE:	08/13/2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Potiga (ezogabine) to ensure that the benefits of the drug outweigh the increased risk of: 1) (b) (4) 2) urinary retention and its associated morbidities. In reaching this determination, we considered the following:

A. It is not possible to estimate precisely the size of the population likely to use Potiga (ezogabine). The estimated number of patients in the United States with partial-onset seizures is approximately 0.9 to 1.8 million. This estimate is based on a US population of about 300 million. The prevalence of epilepsy has been estimated to be 5-10 persons per 1000,[1] with about 60% of these patients having partial seizures.[2]

B. Patients with epilepsy have approximately two to three times the risk of death from any cause compared with persons without epilepsy.[1] Seizures may cause significant trauma, drowning, and accidental injury. Many of the deaths in persons with epilepsy are directly related to seizures, accidents, and injuries arising from seizures, and the

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[1] Harrison's Principles of Internal Medicine, 17th Ed. (2008).
[2] Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. *Mayo Clin Proc*. 1996;71:576–86.

underlying condition resulting in seizures.

C. The efficacy of Potiga (ezogabine) for the adjunctive treatment of partial onset seizures in "refractory[3]" patients was demonstrated in 3 adequate, double-blind, placebo-controlled trials that showed a consistent treatment effect (drug-placebo) of a greater then 20% reduction in seizure frequency.

D. If approved, Potiga (ezogabine) will be administered on a chronic basis to patients with epilepsy.

E. Potiga (ezogabine) use is associated with serious risks:

- *Suicidal Thoughts and Behavior:* A known serious risk of AEDs as a therapeutic class is an increased risk of suicidal thoughts and behavior (which are risk factors for completed suicide). The increased risk of suicidal thoughts and behavior were demonstrated in a meta-analysis of randomized, placebo-controlled clinical trial data for 11 AEDs.

  In this meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66); 0.37% of all drug-treated patients and 0.24% of placebo-treated patients had an event of suicidal behavior or ideation. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all antiepileptic drugs regardless of indication of use.

  The background incidence of suicide in patients with epilepsy is estimated as being higher than the incidence of suicide in the general population. Estimates of the incidence of suicide in patients with epilepsy vary widely, but studies have consistently indicated a higher incidence of suicide (and suicide attempts) in patients with epilepsy.

- *Urinary Retention:* Serious urinary retention resulting in profound morbidity was an early finding in non-clinical studies of ezogabine in rodents. This signal was confirmed in clinical trials with an increased incidence of adverse events classified as urinary retention in the drug versus placebo group. Post-voiding residuals varied from 100 to greater then 1,000 mL. Some cases of urinary retention required drug discontinuation, hospitalization, and/or catheterization. These cases occurred despite the high level of suspicion and the active monitoring for symptoms of retention and post-voiding residuals. Discontinuation of the drug, in all but one case, resulted in a return to normal bladder function. Other potentially associated morbidities included transient creatinine increases, hydronephrosis, and urinary tract infections.

Potiga (ezogabine) has also been associated with other serious adverse effects that include somnolence, dizziness, visual changes (diplopia and blurred vision), psychosis, and encephalopathy/confusional state.

[3] Patients were selected based upon continued seizure activity despite a history of treatment with a number of other anticonvulsants.

F. Potiga (ezogabine) is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Potiga (ezogabine). 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 events. FDA has also determined that Potiga (ezogabine) 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).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

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

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/s/

ELLIS F UNGER
08/16/2010