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APPLICATION NUMBER:

022345Orig1s000

OTHER REVIEW(S)

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 022345
APPLICANT	Valeant Pharm N.A.
PRODUCT NAME	Potiga (ezogabine)
SUBMISSION DATE	15 April 2011
PDUFA DATE	15 June 2011
SEALD SIGN-OFF DATE	10 June 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Laurie Burke

This memo confirms that no critical prescribing information (PI) deficiencies were noted in the SEALD Labeling Review filed 8 June 2011 and no critical deficiencies have been found in the final agreed-upon PI reviewed today. SEALD has no objection to PI approval at this time.

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/s/

LAURIE B BURKE
06/10/2011

**Potiga PMR/PMC Development Template: PREA Efficacy/Safety Study for Ezogabine
PMR # 1**

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

PMR/PMC Description: Prospective, randomized, placebo-control, double-blinded efficacy/ safety trial of Potiga (ezogabine) in children ≥ 12 years old.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>11/2012</u>
	Study/Clinical trial Completion Date:	<u>01/2018</u>
	Final Report Submission Date:	<u>05/2018</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is part of a PREA requirement. It requires a randomized, placebo-control, double-blinded efficacy/ safety and long-term open label study in children ≥ 12 years old. Development in children 1 month to < 12 years is being deferred. The Sponsor has been requested to provide a justification and plan for investigating these younger patients. Moreover, presently studies in younger patients are on hold because of the urologic complications of this disorder. The Division believes there is an increased pediatric risk for urologic complications in these younger patients. This is based upon nonclinical findings in young animals and the difficulty in monitoring urologic function in young pediatric patients. Pediatric studies in patients < 1 month are being waived as partial seizures cannot always be adequately diagnosed or identified in this population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This is to examine efficacy and safety of ezogabine as the adjunctive treatment in an older pediatric population of ≥ 12 years old. The goals are routine except, because of the urologic toxicity, the Sponsor will be asked to include design element so as to protect subjects enrolled from urologic injury as well as provide adequate information on the urologic safety of this drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
 Two prospective studies are being requested in children ≥ 12 years of age.: 1) randomized, placebo-control, double-blinded efficacy/safety and, 2) long-term open label study.
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

**Potiga PMR/PMC Development Template: PREA Long-Term Safety Study for Ezogabine
PMR # 2**

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

PMR/PMC Description: Long-term open label study of ezogabine in children ≥ 12 years old.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>08/2011</u>
	Study/Clinical trial Completion Date:	<u>07/2019</u>
	Final Report Submission Date:	<u>11/2019</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is part of a PREA requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is to examine long-term safety of ezogabine as the adjunctive treatment in an older pediatric population of ≥ 12 years old. The study’s goals are routine except, because of the urologic toxicity, the Sponsor will be asked to include design element so as to protect subjects enrolled from urologic injury as well as provide adequate information on the urologic safety of this drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
 Two prospective studies are being requested in children ≥ 12 : 1) randomized, placebo-control, double-blinded efficacy/safety and, 2) long-term open label study.
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

**Potiga PMR/PMC Development Template Prospective Cohort Study to Examine Urinary Retention
PMR # 3**

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

PMR/PMC Description: Prospective Cohort Study to Examine Urinary Retention

PMR/PMC Schedule Milestones: Final protocol Submission Date: 05/2012
Study/Clinical trial Completion Date: 09/2014
Final Report Submission Date: 11/2014
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☒ Long-term data needed
☒ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☒ Other

Urinary retention, through ezogabine effect on the bladder, was identified as an issue during drug development. While it is believed that urinary retention can be managed through the use of a MedGuide and communication plan, it is felt that additional information may provide more information to allow for better management his risk.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Urinary retention has been described significant adverse reaction associated with the use of ezogabine. While some factors may be theoretically associated with an increased risk, such as the use of other medication or preexisting conditions that may influence urinary function, these have not been well defined. Moreover, clinical trials were not of sufficient size or duration to obtain a definitive estimate of risk as compared to other anticonvulsants. The present proposed studies will better define these issues.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☒ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Potiga PMR/PMC Development Template

Potiga PMR # 4

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

PMR/PMC Description: In vitro study to evaluate whether ezogabine is a substrate for major transporters in kidney

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>09/2011</u>
	Study/Clinical trial Completion Date:	<u>10/2011</u>
	Final Report Submission Date:	<u>11/2011</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

This PMR is for an in vitro study to investigate whether ezogabine is a substrate for major transporters in kidney. This can be done post-marketing as the uncertainty is described in the label.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has not conducted an in vitro study to investigate whether ezogabine is a substrate for transporters, other than P-glycoprotein, in kidney. Renal elimination is the major route of elimination for ezogabine, and ezogabine is actively secreted in urine. There is a theoretical concern for significantly increased systemic exposure of ezogabine in the presence of concomitant medications that are inhibitors or inducers of certain transporters for which ezogabine could be a substrate, and this potential increased exposure could result in safety concerns. The goal of this study is to evaluate whether ezogabine is a substrate for the major transporters in kidney. Based on the results of the study, an in vivo study may be required. The Sponsor should refer to the Agency's Guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf>) for more detailed recommendations regarding transporter-based drug-drug interactions.

NDA 22345

Potiga

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Potiga PMR/PMC Development Template
Potiga PMR #5

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

PMR/PMC Description: *An in vitro* study to evaluate the potential for ezogabine to inhibit CYP2B6.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>09/2011</u>
	Study/Clinical trial Completion Date:	<u>10/2011</u>
	Final Report Submission Date:	<u>11/2011</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☒ Other

This PMR to screen for the potential for ezogabine to inhibit CYP2B6 using recommended probe substrates can be done postmarketing as the uncertainty is described in the label.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has not conducted an vitro study to investigate the potential for ezogabine to inhibit CYP2B6. There is a theoretical concern for increased systemic exposure of concomitant medications that are CYP2B6 substrates and consequent safety concerns if ezogabine inhibits CYP2B6. The goal of this study is to evaluate the potential for ezogabine to inhibit CYP2B6. Based on the results of the study, an in vivo study may be required.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for Ezogabine

PMR # 6

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

PMR/PMC Description: An animal study to examine for possible withdrawal symptoms that may be indicative of physical dependence.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>11/2011</u>
	Study/Clinical trial Completion Date:	<u>01/2012</u>
	Final Report Submission Date:	<u>05/2012</u>
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Physical dependence is a physiological adaptation resulting from repeated use of a drug. The assessment of physical dependence is a critical evaluation for all CNS-active drugs in order to determine appropriate drug discontinuation and management of withdrawal signs and symptoms, if present. Thus, evaluation of physical dependence provides important information about the circumstances impacting safe use of a drug.

Typically, physical dependence is assessed in both animal and human studies using abrupt drug discontinuation. However, in patients with epilepsy, abrupt discontinuation of antiepileptic drugs such as ezogabine can produce severe AEs, including the return of epileptic seizures and their sequelae. This is an unacceptable safety concern. Similarly, conducting a physical dependence study with ezogabine in healthy subjects exposes subjects to a drug that can produce serious adverse events (including psychotic disorder and atrial fibrillation) without any potential benefit for these subjects. This is also an unacceptable safety concern. Since a physical dependence study cannot be conducted safely in a patient population or in a healthy subject population, an animal physical dependence study is required to evaluate physical dependence. Although results of the study will provide more information to allow for better management of the risk, it is believed that the risk of physical dependence can be addressed through the use of a Medication Guide based on currently available data"?)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the animal physical dependence study is to determine whether chronic administration of ezogabine produces a withdrawal syndrome following drug discontinuation.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
 - ☐ Registry studies
 - ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Potiga PMR/PMC Development Template
PMR # 7

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

PMR/PMC Description: Urodynamic trial

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>11/2011</u>
	Study/Clinical trial Completion Date:	<u>07/2015</u>
	Final Report Submission Date:	<u>11/2015</u>
	Other:	<u></u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Urinary retention, through ezogabine effect on the bladder, was identified as an issue during drug development. While it is believed that urinary retention can be managed through the use of a MedGuide and communication plan, it is felt that additional information may provide more information to allow for better management his risk. This was a recommendation made by our advisory board (see response to item #2).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

While Ezogabine’s effect on the bladder is assumed to be mediated by its ability to open potassium channels and to therefore relax the detrusor muscle, this mechanism has not been established in human subjects. The urologists on the advisory committee convened to examine the urologic issues of ezogabine were impressed by the unpredictable nature of the urinary retention adverse events in the Ezogabine clinical trials, and believed that an understanding of the mechanism of this drug’s direct effect on the lower urinary track function in humans might provide a better strategy for risk management. The currently proposed mechanism of action is largely focused on motor function of the bladder smooth muscle; however, one urologist on the advisory committee speculated that the variable presentation of urinary retention may be consistent with an effect on the sensory and not the motor arm of bladder function control. This study would elucidate this.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☒ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Potiga PMR/PMC Development Template
PMR #8

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

PMR/PMC Description: A clinical trial to evaluate the acetyl metabolite of ezogabine (NAMR) as an inhibitor of P-glycoprotein (P-gp) using digoxin as a probe substrate.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>11/2011</u>
	Study/Clinical trial Completion Date:	<u>04/2012</u>
	Final Report Submission Date:	<u>08/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This PMR is for a clinical trial to investigate the impact of the acetyl metabolite of ezogabine (NAMR) as an inhibitor of P-glycoprotein (P-gp) using digoxin as a probe substrate. This can be done post-marketing, as NAMR was shown to be an inhibitor for P-gp transport activity in vitro and the potential for drug-drug interactions with concomitant administration of ezogabine with medications that are P-gp substrates, such as digoxin, is described in the label based on the results of the in vitro study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Based on an in vitro study, the acetyl metabolite of ezogabine (NAMR) was found to be an inhibitor of the efflux transporter P-gp at therapeutic levels of ezogabine. This inhibition can result in a decrease of renal clearance of digoxin and hence an increase in systemic exposure. This potential interaction is described in the label. However, a study in humans has not been conducted to quantitatively evaluate the extent of this potential drug-drug interaction for digoxin to help guide the dosage adjustment when ezogabine is co-administered with medications that are P-gp substrates, such as digoxin. A drug interaction with digoxin (a drug with narrow therapeutic index) would result in safety concerns for the patients. Therefore, the goal of this trial is to evaluate the impact of ezogabine (or NAMR) on transport activity of P-gp, using digoxin as probe substrate, in humans. The Sponsor should refer to the Agency's Guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf>) for more detailed recommendation regarding transporter-based drug-drug interactions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

SALLY U YASUDA
06/09/2011
completed PMR templates

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 022345
APPLICANT	Valeant Pharmaceuticals North America
PRODUCT NAME	Potiga (ezogabine)
SUBMISSION DATE	April 15, 2011
PDUFA DATE	June 15, 2011
SEALD REVIEW DATE	June 8, 2011
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- ☐ There is no redundancy of information.
- ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- ☐ A horizontal line must separate the HL and Table of Contents (TOC).
- ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- ☐ Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- ☐ Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- ☐ The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- ☐ All text in the boxed warning is **bolded**.
- ☐ Summary of the warning must not exceed a length of 20 lines.
- ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- ☐ Must have the verbatim statement “***See full prescribing information for complete boxed warning.***” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- ☐ Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- ☐ All contraindications listed in the FPI must also be listed in HL.
- ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- ☐ A horizontal line must separate the TOC and FPI.
- ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- ☐ For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- ☐ For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- ☐ This section is required and cannot be omitted.
- ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

JUN YAN

06/08/2011

No SRPI issues on the agreed-upon draft PI.



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

Date: June 7, 2011

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Lori Love, M.D., Ph.D., Lead Medical Officer
Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Ezogabine (Potiga) NDA 22-345, Review of Drug Abuse
and Dependence section of label
Indication: Adjunct treatment of partial-onset seizures
Dosages: 200-400 mg TID; 600-1200 mg/day
Sponsor: Valeant Pharmaceuticals, North America

Materials reviewed: Sponsor-proposed label text in NDA resubmission

Table of Contents

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I. Summary

A. Background:

The Division of Neurology Products (DNP) consulted CSS regarding the Sponsor-proposed label text for Potiga (ezogabine), a drug that is indicated as an adjunct treatment for partial-onset seizures. Ezogabine acts by enhancing currents mediated by four potassium KCNQ channel subtypes (2, 3, 4, 5), as well as currents mediated by neuronal KCNQ2/3 channels. The Sponsor received a Complete Response (CR) letter for the NDA on November 30, 2010. On April 15, 2011, the Sponsor resubmitted a revised NDA, which was accepted by DNP as a complete response with a revised PDUFA date of June 15, 2011. Our current comments address the Drug Abuse and Dependence section of the Sponsor-proposed label text.

B. Conclusion:

The Sponsor-proposed text changes (described below in Discussion) are acceptable with the exception noted below.

C. Recommendation:

In Section 9.3 Dependence, the drug should be identified as “ezogabine,” rather than as “POTIGA” as proposed by the Sponsor, for consistency with the remainder of the text in Section 9.0.

II. Discussion

Our review of the Sponsor-proposed text for the Drug Abuse and Dependence section (Section 9.0) of the drug label for Potiga (ezogabine) shows the following changes:

(b) (4)

Thus, the label text should read as follows:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

[Note to Sponsor: A statement about scheduling will be added after a final scheduling action by DEA.]

9.2 Abuse

A human abuse potential study was conducted in recreational sedative-hypnotic abusers (n = 36) in which single oral doses of ezogabine (300 [n = 33], 600 [n = 34], 900 mg [n = 6]), the sedative-hypnotic alprazolam (1.5 and 3.0 mg), and placebo were administered. Euphoria-type subjective responses to the 300- and 600-mg doses of ezogabine were statistically different from placebo but statistically indistinguishable from those produced by either dose of alprazolam. Adverse events reported following administration of single oral doses of 300, 600, and 900 mg ezogabine given without titration included euphoric mood (18%, 21%, and 33%, respectively; 8% from placebo), hallucination (0%, 0%, and 17%, respectively; 0% from placebo) and somnolence (18%, 15%, and 67%, respectively; 15% from placebo).

In Phase 1 clinical studies, healthy individuals who received oral ezogabine (200 to 1,650 mg) reported euphoria (8.5%), feeling drunk (5.5%), hallucination (5.1%), disorientation (1.7%), and feeling abnormal (1.5%).

In the 3 randomized, double-blind, placebo-controlled Phase 2 and 3 clinical studies, patients with partial seizures who received oral ezogabine (300 to 1,200 mg) reported euphoric mood (0.5%) and feeling drunk (0.9%), while those who received placebo did not report either adverse event (0%).

9.3 Dependence

There are no adequate data to assess the ability of ezogabine to induce symptoms of withdrawal indicative of physical dependence. However, the ability of ezogabine to produce psychological dependence is suggested by adverse event reports of euphoric mood (18% [6 of 33 subjects] to 33% [2 of 6 subjects]) in sedative-hypnotic abusers in the human abuse potential study and adverse event reports of euphoria (8.5%) in healthy individuals who participated in Phase 1 studies.

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/s/

KATHERINE R BONSON
06/07/2011

LORI A LOVE
06/07/2011

MICHAEL KLEIN
06/07/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: May 10, 2011

To: Karen Abraham-Burrell
Regulatory Project Manager
Division of Neurology Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Robyn Tyler, Acting Group II Leader, DDMAC

Subject: NDA 022345
DDMAC Comments for Potiga (ezogabine) Tablets
Medication Guide

DDMAC has reviewed the proposed Medication Guide (MG) for Potiga. We also reviewed the comments on this MG from the Division of Risk Management (DRISK) dated May 10, 2011. We agree with DRISK's comments and offer the following additional comments.

DDMAC's comments are provided directly on the clean copy of DRISK's version of the MG.

Thank you for the opportunity to comment on the proposed Medication Guide.

If you have any questions or concerns regarding my comments, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
05/10/2011

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

PATIENT LABELING REVIEW

Date: **May 9, 2011**

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management (DRISK)

Melissa Hulett, MSBA, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): POTIGA (ezogabine)

Dosage Form and Route: Tablets

Application Type/Number: NDA 22-345

Applicant: Valeant Pharmaceuticals North America LLC

OSE RCM #: 2011-1284

1 INTRODUCTION

Valeant Pharmaceuticals North America LLC submitted a New Drug Application (NDA) for Potiga (ezogabine) Tablets on October 30, 2009 for the proposed indication of adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy aged 18 years and older.

On August 16, 2010 DNP issued a Pre-Approval REMS Notification letter stating that a REMS with a MG and a CP was required for approval. The applicant submitted a proposed REMS August 26, 2010.

On November 30, 2010, the Division of Neurology Products issued a Complete Response (CR) letter due to outstanding nonclinical, biopharmaceutical, labeling, risk evaluation and mitigation strategy requirements, and safety update deficiencies. This CR acknowledged the REMS submission and stated that the discussion of the proposed REMS would continue after the CR was submitted.

On April 15, 2011, Valeant Pharmaceuticals North America LLC resubmitted the application addressing deficiencies communicated in the CR letter.

On Friday, February 25, 2011, FDA published a draft Guidance that addresses when a Medication Guide will be required as part of a REMS. Based on the risks of a drug and public health concerns, FDA has the authority to determine whether a Medication Guide should be required as part of a REMS or should be required as labeling but not part of a REMS.

On May 5, 2011 DRISK and DNP met to discuss the proposed REMS submission. It was agreed that the REMS would be a Communication Plan and that the MG would be approved labeling and not part of the REMS. The REMS will be reviewed under separate cover. Therefore, this review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Potiga (ezogabine) Tablets.

2 MATERIAL REVIEWED

- Draft Potiga (ezogabine) Tablets, Medication Guide (MG) received on April 15, 2011, revised by the Review Division throughout the current review cycle and sent to DRISK on April 26, 2011.
- Draft Potiga (ezogabine) Tablets, Prescribing Information (PI) received on April 15, 2011, revised by the Review Division throughout the current review cycle and sent to DRISK on April 26, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published

Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS TO DNP

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
05/09/2011

LASHAWN M GRIFFITHS
05/09/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

******Pre-decisional Agency Information******

Memorandum

Date: 12/16/10

To: Stephanie Keefe, Regulatory Project Manager
Division of Neurology Products (DNP)

From: Quynh-Van Tran, Regulatory Review Officer
Beth Carr, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: NDA 022345
DDMAC labeling Comments for Potiga® (ezogabine) tablet

We acknowledge receipt of your January 12, 2010, consult request for the proposed product labeling for Potiga® (ezogabine) tablet, NDA 022345. DDMAC notes that a Complete Response letter was issued on November 30, 2010 and final labeling negotiation was not initiated during the current review cycle. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle.

DDMAC requests that DNP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials. If you have any questions, please contact Quynh-Van Tran at 301-796-0185 or Beth Carr at 301-796-3674.

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/s/

BETH M CARR
12/17/2010

DSI CONSULT: Request for Clinical Inspections

Date: December 14, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Antoine El Hage
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Steven Dinsmore, D.O., Medical Officer, DNP*
Norman Hershkowitz, M.D., Neurology Team Leader, DNP
Russell Katz, M.D., Director, DNP

From: *Stephanie N. Keefe, Regulatory Health Project Manager/DNP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22-345
Applicant: Valeant Pharmaceuticals North America
Contact: Susan T. Hall, Ph.D. 919-294-3070
Drug Proprietary Name: Potiga
NME(Yes/No): Yes
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Adjunctive therapy in refractory epilepsy patients with partial-onset seizures

PDUFA:
Action Goal Date: August 30, 2010
Inspection Summary Goal Date: June 30, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site # 001 Dr. Bassell Abou-Khalil Phone 615-935-2591 Vanderbilt Univ. Med. Ctr. Department of Neurology 1161 21st Avenue South A-0118 Medical Center North Nashville, TN 37232 USA	VRX-RET-E22-301	20	Largest US enrollment
Site # 107 Dr. Albino Contreras-Milian Phone +52(81) 8346-1160 Hospital y Clinica OCA / MIRC Pablo A. Gonzalez 709 Col. Mitras Sur Monterrey, NL 64020 MEXICO	VRX-RET-E22-301	12	Large enrollment with 2 protocol violations
Site # 401 Prof. Christian Erich Elger Klinik und Poliklinik für Epileptologie Sigmund-Freud-Str. 25 Bonn, NW 53127 GERMANY	VRX-RET-E22-302	38	Largest study 302 enrollment
Site # 853 Dr. Sergiy Kharchuk Phone +38(044) 468-0417 Epilepsy Center of Municipal Clinical Psychoneurological Hos epileptology dept. Frunze str. 103-A Kiev 04080 UKRAINE	VRX-RET-E22-302	24	Two operational protocol violations, insufficient baseline seizures for inclusion. 3 rd largest enrollment of study 302

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ☒ Enrollment of large numbers of study subjects
- ☐ High treatment responders (specify):
- ☐ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ☐ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- ☒ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☐ Domestic and foreign data show conflicting results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ☒ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Stephanie N. Keefe, RPM*, at 301-796-4098 or *Steven Dinsmore, D.O.*, at 301-796-4155.

Concurrence: (as needed)

_____X_____	Medical Team Leader
_____X_____	Medical Reviewer
_____X_____	Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/

STEPHANIE N KEEFE
01/04/2010

RUSSELL G KATZ
01/04/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 03, 2010

TO: Russell G. Katz, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation-I

FROM: Sripal R. Mada, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 12/3/10*
Acting Team Leader, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Addendum to the review of EIR Covering NDA 22-345,
Potiga (Retigabine) Tablets, 50, (b) (4) 200, 300 and 400
mg, Sponsored by Valeant Pharmaceuticals, N.A.

At the request of Division of Neurology Products (DNP), the Division of Scientific Investigations (DSI) conducted an audit of both clinical and bioanalytical portions of the following bioequivalence study.

Study Number: RTG113287

Study Title: "An open-label, single-centre, randomized, 2-way crossover study to evaluate the bioequivalence of retigabine given as the Market Image tablet compared to retigabine clinical trial tablet"

DSI sent an inspection summary memo for the above audit to DNP on August 25, 2010. DSI recommended that the discrepancies concerning the drug accountability issue under clinical finding need to be resolved prior to accepting the data from the study RTG113287 for the review.

This addendum is to inform DNP that DSI received the firm's response (dated September 03, 2010) on September 07, 2010 (see **Attachment-1**). Following our review, DSI finds the firm's response to be adequate and the study RTG113287 be accepted for review.

Page 2 - NDA 22-345, Potiga (Retigabine) Tablets, 50 mg, (b) (4)
200 mg, 300 mg, and 400 mg,

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Sripal R. Mada, Ph.D.

Final Classification:

VAI - Charles River Clinical Services Northwest, Tacoma, WA
FEI: 3002998793

VAI - (b) (4)

FEI: (b) (4)

cc:

DSI/Ball

DSI/GLPBB/Haidar/Yau/Patel/Mada

OND/DNP/Keefe/Katz

OCP/DCP-1/Wu/Men

HFR-PA350/Brown

Draft: SRM 12/03/2010

Edit: MKY 12/03/2010

File:6067 O:\BE\EIRCOVER\22345val.pot.addendum1.doc

FACTS 1167359

Email:

CDER DSI PM TRACK

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/s/

SRIPAL R MADA

12/06/2010

Original signed documents are available in the DSI file

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

Date: November 9, 2010
Application Type/Number: NDA 022345
To: Russell Katz, MD, Director
Division of Neurology Products
Through: Zachary Oleszczuk, Pharm.D., Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis
From: Manizheh Siahpoushan, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): Potiga (Ezogabine) Tablets
Applicant/sponsor: Valent Pharmaceuticals
OSE RCM #: 2009-2278-1

1 INTRODUCTION

This review responds to a request from the Division of Neurology Products (DNP) for a review of the revised labels and labeling of Potiga submitted on October 8, 2010. These revisions were made in response to comments from the Division of Medication Error Prevention and Analysis in OSE Review #2009-2278, dated August 13, 2010. In that review DMEPA recommended increasing the color differentiation between each of the five strengths by presenting the strength in a separate font color, distinct from the color used to present the proprietary name as well as deleting the color background presented behind the tablet pictures for the 50 mg and (b) (4) strengths. Additionally, DMEPA suggested revisions to the titration pack to clarify information such as the net quantity and dosing instruction and to better define each day of therapy by separating each day with a solid black line.

2 MATERIAL REVIEWED

The Applicant provided revised container label and carton labeling on October 8, 2010, for the 50 mg, (b) (4) 200 mg, 300 mg, 400 mg strengths and the titration pack (see Appendices A and B). We also evaluated the recommendations from OSE Review #2009-2278, dated August 13, 2010, to ensure that all DMEPA recommendations have been incorporated into the revised labels and labeling.

3 RESULTS AND DISCUSSION

Review of the revised labels and labeling show that the Applicant implemented DMEPA's recommendations from OSE Review #2009-2278, dated August 13, 2010, on improving color contrast regarding the strength and background presentation. The applicant has also addressed all the revisions recommended by DMEPA for the Titration Pack (outside & inside panels).

4 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address DMEPA's concerns and DMEPA has no further comments at this time. If you have further questions or need clarifications, please contact Laurie Kelley, OSE Project Manager, at 301-796-5068.

5 REFERENCES

*OSE Review #2009-2278, Label and Labeling Review for Potiga Tablets. Turner,T:
August 13,, 2010.*

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/s/

MANIZHEH SIAHPOUSHAN
11/09/2010

ZACHARY A OLESZCZUK
11/09/2010

DENISE P TOYER
11/10/2010

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

Date: October 13, 2010

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management (DRISK)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): Potiga (ezogabine) Tablets

Application Type/Number: NDA 22-345

Applicant/sponsor: Valeant Pharmaceuticals North America

OSE RCM #: 2009-2345

1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Potiga (ezogabine) Tablets. The proposed REMS is being reviewed by DRISK and will be provided to DNP under separate cover.

Valeant Pharmaceuticals North America submitted a New Drug Application (NDA) for Potiga (ezogabine) Tablets on October 30, 2009 for the proposed indication of adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy aged 18 years and older.

Please let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Potiga (ezogabine) Tablets Prescribing Information (PI) submitted on July 26, 2010, revised by the Review Division throughout the current review cycle and received by DRISK on September 21, 2010.
- Draft Potiga (ezogabine) Tablet Medication Guide (MG) submitted on July 26, 2010 and received by DRISK on September 21, 2010.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG is consistent with other product labels in the same drug class where applicable.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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/s/

BARBARA A FULLER
10/14/2010

LASHAWN M GRIFFITHS
10/14/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 25, 2010

TO: Russell G. Katz
Director, Division of Neurology Products (DNP)

FROM: Jyoti B. Patel, Ph.D.
Sam Haidar, Ph.D.
Martin K. Yau, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 8/25/10*
Acting Team Leader, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-345,
Potiga (Retigabine) Tablets, 50 mg, (b) (4) 200 mg,
300 mg, and 400 mg, Sponsored by Valeant
Pharmaceuticals, North America

At the request of Division of Neurology Products (DNP) and Office of Clinical Pharmacology (OCP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and bioanalytical portions of the following bioequivalence study.

Study Number: **RTG113287**

Study Title: "An open-label, single-centre, randomized, 2-way crossover study to evaluate the bioequivalence of retigabine given as the Market Image tablet compared to retigabine clinical trial tablet"

The clinical and analytical portions of Study RTG113287 were conducted on May 6 - 13, 2010 at Charles River Clinical Services Northwest, Tacoma, Washington (Charles River) and on July 12-15, 2010 at (b) (4) respectively.

Following the inspections, Form FDA-483 was issued at both the clinical and analytical sites (Attachments 1 and 2). Charles River (clinical site) and (b) (4) (bioanalytical site) responded to

the Form FDA-483 observations in letters dated June 4, 2010 and August 4, 2010 respectively (Attachments 3 and 4). The Form FDA-483 observations, written responses by the sites, and our evaluations are as follows:

Form FDA-483 Clinical Observation issued at Charles River Clinical Services Northwest, Tacoma, Washington:

Clinical 483 Observation 1:

An investigation was not conducted in accordance with the investigational plan.

Specifically, four out of six consecutive subjects (#177, #178, #179 and #180) did not have the required 2-hour time point blood draw for a pharmacokinetic (PK) study on August 22, 2009. This failure to perform the study procedure was due to the use of a staffing grid or schedule, which failed to include the required 2-hour time-point blood draw.

In response to this observation, Charles River acknowledged that the schedule used for the 2-hr PK draw was not completely accurate thereby contributing to a missed draw for the 4 subjects. A standard operating procedure will be created to effectively manage the review and control of the scheduling of staff as part of the corrective action. The SOP and all the related training will be completed in the 3rd quarter of 2010.

Other Clinical Findings

Please note that in addition to the above Form FDA-483 observation, there were three discussion items (see Attachment 3 and 5 for details) in the Establishment Inspection Report (EIR). Following a review of the discussion items, DSI found that the discussion items should have no significant impact on the study outcomes.

However, it should be noted that after the close of the inspection, the FDA field investigator noticed that there were discrepancies in the drug accountability records regarding the 50 mg clinical trial retigabine tablets, and she documented these discrepancies in the EIR, but this finding was not put on the Form FDA-483. Specifically, 8 bottles of 50 mg (b) (4), 6 bottles each of the 300 and 400 mg retigabine tablets (b) (4) were received by Charles River. According to the EIR, the Pharmacy Drug Accountability records showed that two 50 mg tablets were

dispensed to each subject for study treatment 'B' (i.e., 2 x 50 mg clinical trial tablets plus 1 x 300 mg clinical trial tablet) and (b) (4) of 50 mg tablets were returned to GSK on December 1, 2009. However, the Investigational Product Accountability/Reconciliation sheet documented that four intact bottles (b) (4) were returned to GSK. Thus, the Investigational Product Accountability/Reconciliation sheet does not agree with the Pharmacy Drug Accountability records. Furthermore, as Charles River also maintained (b) (4) of 50 mg tablet (b) (4) on site as reserve samples, and there were 80 doses of the study treatment 'B' dispensed to subjects (i.e., (b) (4) of 50 tablets would have been consumed), the number of 50 mg clinical trial retigabine tablets dispensed to study subjects, returned to GSK, and maintained as reserve samples at Charles River does not match the total number of 50 mg tablets received. In short, if Charles River received (b) (4) of 50 mg tablets, returned (b) (4) (according to the Pharmacy Drug Accountability records) or (b) (4) (according to Investigational Product Accountability /Reconciliation sheet), and kept (b) (4) as reserve samples, then Charles River could not have dispensed two 50 mg tablets per subject

As the above finding regarding drug accountability raised questions concerning the accuracy of dosing for study treatment 'B', Charles River needs to resolve the drug accountability/reconciliation discrepancies. Also, please note that DSI has discussed the above discrepancies with the FDA field investigator on 8/24/10 and she has agreed to return to Charles River on 8/26/10 to issue a Form FDA-483 for this finding.

Form FDA-483 Analytical Observations issued at (b) (4)
Bioanalytical Lab.:

Analytical Observation 1:

Failure to justify and document properly the conduct of (b) (4) all validation and analytical runs in Study RTG113287.

(b) (4)

(b) (4)

In response to this observation, (b) (4) acknowledged that there was no written procedure or SOP in place for the selection of samples to be injected while assessing system suitability prior to initiation of the actual study run. In the cases highlighted above, inclusion of actual study samples was not intentional; sample selection was random and based strictly on (b) (4)

(b) (4) In the instances where study samples were injected they generally included the first 1 to 4 samples in the PK sampling time course for the first subject contained on the plate.

(b) (4)

Overall, DSI is of the opinion that the response from (b) (4) is adequate.

Analytical Observation 2:

Failure to develop a written procedure for analysts to set unbiased integration parameters for analytical runs.

Specifically, (b) (4)

(b) (4) acknowledged that there was no written procedure or SOP in place for setting and applying integration parameters to analytical runs. In response to the FDA 483, (b) (4) retrospectively applied the same optimized integration parameters established

during method validation to all analytical runs. After

(b) (4)

As a corrective measure (b) (4) will develop a documented procedure and put in place the procedure that details the selection of initial integration parameters for an unbiased integration of the chromatograms. This will be completed by September 30, 2010 and any changes to the initial set of parameters will be justified and document within the study. DSI accepts their response

Analytical 483 Observation 3:

Failure to store study plasma samples in a secure and controlled environment.

(b) (4)

Analytical 483 Observation 4:

Failure to conduct partial assay re-validation when a different mass spectrometer (i.e. (b) (4)) was employed in the retigabine assay.

(b) (4) acknowledged that a partial validation between the mass spectrometers was not conducted during the analysis of samples from study RTG113287. In response to the FDA 483 observation, (b) (4)

(b) (4) The results of the partial validation provided in the written response indicate that the bioanalytical method can be used with either a (b) (4)

(b) (4). An update will be made to the method
validation SOP by September 30, 2010 (b) (4)l

(b) (4) n
DSI accepts
their response

Analytical 483 Observation 5:

Failure to perform calibration and daily and preventive
maintenance of analytical instruments used in the analysis of
bioanalytical samples obtained in Study RTG113287. Specifically:

- a. The last annual preventive maintenance of the (b) (4)
(b) (4) systems was conducted on 8/6/08; the firm began
sample analysis on 8/26/09 and completed analysis on 10/5/09.
- b. Documentation of daily maintenance of the instruments is not
available for the study time period, including the System
Maintenance Log for (b) (4) and the Instrument Condition Log
for (b) (4) is not available for WWUM12.

(b) (4)

- b. The documentation for daily maintenance of the above
instruments during the study period cannot be located. GSK
will evaluate their process for managing daily instrument
maintenance documentation and put controls in place to ensure
that this documentation does not get misplaced in the future.

Analytical 483 Observation 6:

Failure to document in the study record the analytical equipment
used in the preparation and analysis of bioanalytical samples,
including (b) (4).

In response to this observation, (b) (4) agrees that all major items
of equipment, (b) (4) (b) (4) (b) (4)

used in sample analysis will be uniquely identified and documented in the study file starting August 31, 2010.

Conclusion

Following the inspections at Charles River (clinical site) and (b) (4) (analytical site), DSI recommends that the discrepancies concerning the drug accountability issue (see discussion under 'Other Clinical Findings') be resolved prior to accepting the data from study RTG113287 for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Jyoti B. Patel, Ph.D.
Staff Fellow (Pharmacologist)

DSI Final Classification:

VAI - Charles River Clinical Services Northwest, Tacoma, Washington

VAI - (b) (4)

CC:

CDER DSI PM TRACK
OC DSI/Ball/Haidar/Yau/Patel/Rivera-Lopez/CF
OND/ODEI/DNP/Stephanie Keefe
OTS/OCP/DCP1/Ta-Chen Wu
OTS/OCP/DCP5/Angela Men
HFR-PA350/Carol Gripp (BIMO)/S. Lori Brown
Draft: JBP 8/23/2010
Edit: MKY 8/23/2010, 8/24/10
File: 6067 O:\BE\EIRCOVER\22345val.pot.doc
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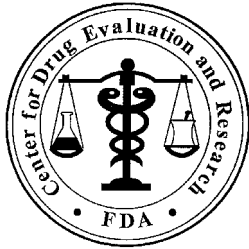
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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

/s/

JYOTI B PATEL
08/25/2010

Dr. Martin Yau and Dr. Jyoti Patel signed the paper copy on August 25, 2010. Original signed copies are available in the DSI file



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

Date: August 13, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Zachary Oleszczuk, Pharm.D., Acting Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

From: Tara Turner, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Potiga (Ezogabine) Tablets
50 mg, (b) (4) 200 mg, 300 mg, and 400 mg

Application Type/Number: NDA 022345

Applicant: Valeant Pharmaceuticals North America

OSE RCM #: 2009-2278

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1 INTRODUCTION

This review responds to a request from the Division of Neurology Products (DNP) for evaluation of the labels and labeling of Potiga to identify areas that could contribute to medication errors. The Applicant submitted proposed container labels, carton and insert labeling for our review and comment.

1.1 REGULATORY HISTORY

The proposed proprietary name, Potiga, was originally submitted to IND 053950. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed and had no objection to the proposed name in OSE Review # 2008-2021 dated May 5, 2009. NDA 022345 for Potiga was submitted on October 30, 2009. As such, the proposed name was submitted to the NDA for re-review on November 20, 2009. DMEPA found the name acceptable on re-review (OSE Review # 2009-2277 dated February 18, 2010) and communicated this finding to the Applicant in a letter dated February 18, 2010.

In the original review of the proposed proprietary name, Potiga, DMEPA identified a concern with the (b) (4). The Division of Neurology Products agreed with our concern and requested that the Applicant petition the United States Adopted Names (USAN) Council for a new established name. In a letter dated November 20, 2009, the Applicant notified FDA of their intent to pursue two alternate established names, (b) (4) and Ezogabine (back-up). In a letter dated April 1, 2010, the Applicant notified FDA of a change in established name for the proposed product. The established name Retigabine was rescinded and the new USAN designated established name is Ezogabine.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and carton labeling submitted May 11, 2010 (see Appendix A) and the insert labeling submitted May 21, 2010. The labels and labeling reflect the new established name, Ezogabine. We also requested a working sample of the titration pack, but have not received it as of the date of this review.

3 RECOMMENDATIONS

Our evaluation of the container labels and carton labeling noted that the color differentiation on the container labels could be enhanced to help minimize the risk of errors resulting from wrong strength selection. Additionally, the dosing instructions in the package insert labeling and on the titration kit could be revised to improve clarity. We provide recommendations for all product labels and labeling in *Section 3.1 Comments to the Division* for discussion during the review team's label and labeling meetings. *Section 3.2 Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Laurie Kelley, Project Manager, at 301-796-5068.

3.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. In the *Dosage and Administration* section of the Highlights of Prescribing Information, the initial dosing instructions are unclear (e.g. 300 mg/day for 1 week). Present the initial dosing instructions using language from the Full Prescribing Information (e.g. The initial dose should be (b) (4) 3 times daily [300 mg/day] for 1 week).
2. In Section 2 *Dosage and Administration* of the Full Prescribing Information, the description of the procedure for discontinuation of Potiga is vague. Provide more specific directions regarding discontinuation, as the data allows.
3. Section 2 *Dosage and Administration* of the Full Prescribing Information does not include (b) (4)

3.2 COMMENTS TO THE APPLICANT

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”.
2. In the box titled “Kit Contains”, change the presentation of the information inside the box to read as follows:

50 mg tablets (quantity 21)

(b) (4)

3. In the box titled “Dosing Instructions”, add the statement “(b) (4)” 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 (b) (4) 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 “Take one tablet”. As currently presented, it reads (b) (4)

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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/

ZACHARY A OLESZCZUK
08/13/2010

DENISE P TOYER
08/13/2010

CAROL A HOLQUIST
08/13/2010

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 6, 2010

TO: Stephanie Keefe, Regulatory Health Project Manager
Steve Desmore, D.O., Medical Officer
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-345

APPLICANT: Valeant Pharmaceuticals North America.

DRUG: Potiga (retigabine)

NME: Yes.

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of patients with partial-onset seizures

CONSULTATION REQUEST DATE: December 14, 2009

DIVISION ACTION GOAL DATE: August 30, 2010

PDUFA DATE: Not listed/assume to be August 30, 2010

I. BACKGROUND:

The Sponsor, Valeant Pharmaceuticals North America, submitted a New Drug Application for the marketing approval of Retigabine (RTG) as adjunctive therapy in patients with refractory epilepsy with partial-onset seizures, with or without secondary generalization.

The results of two pivotal studies were submitted in support of the application:

- Protocol VRX-RET-E22-301 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
- Protocol VRX-RET E22-302 entitled: “A Randomized, Double-Blind, Placebo-Controlled, multicenter, Parallel-Group Phase 3 Study to determine the Efficacy and Safety of Retigabine (900 mg /day and 600 mg/day) used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures ”.

In Study 301, subjects were assigned to receive retigabine at 1200 mg/day (400 mg TID) compared to placebo TID, in addition to their established 1, 2 or 3 antiepileptic drug (AED) regimen. Study Protocol VRX-RET-E22-301’s primary objective was to demonstrate a superior change in total partial seizure frequency per 4 weeks from baseline to the double-blind period (titration through maintenance) in patients treated with retigabine dosed at 1200 mg/day, in 3 equally divided doses compared with placebo.

Study Protocol VRX-RET-E22-301’s key secondary objectives included demonstration of the safety and tolerability of retigabine compared to placebo and demonstration of improvement compared to placebo in the proportion of the responders experiencing a greater than or equal to 50 % reduction in total partial seizure frequency.

In Study 302, subjects were assigned to receive retigabine at either 900 mg daily (300 mg TID) or 600 mg daily (200 mg TID) compared to placebo TID, in addition to their established 1, 2, or 3 AED regimen. The studies enrolled male and female subjects over 18 years of age. The duration of adjunctive therapy included an 18-week maintenance period and a transition phase of additional 6 weeks. A brief description of the study objectives are presented below.

Study Protocol VRX-RET-E22-302’s primary objective was to demonstrate a superior change in total partial seizure frequency per 4 weeks from baseline to the double-blind period in patients treated with retigabine dosed at 900 mg/day, in 3 equally divided doses compared with placebo.

Study Protocol VRX-RET-E22-302’s key secondary objectives included demonstration of the safety and tolerability of retigabine compared to placebo and demonstration of improvement compared to placebo in the proportion of the responders experiencing a greater than or equal to 50 % reduction in total partial seizure frequency from baseline.

The review division requested inspection of four clinical investigators for the two pivotal studies (Protocols VRX-RET-E22-301 and E22-302) as data from the two protocols are considered essential to the approval process. Two foreign clinical investigators and two domestic investigators were chosen to cover the two protocols. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, 2) relatively large number of protocol violations at the sites and 3) these sites demonstrating significant primary efficacy results pertinent to decision-making. This application is a New Molecular Entity and therefore was linked to a sponsor inspection. The sponsor, Valeant Pharmaceuticals North America was also inspected in support of the pending application.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Bassell Abou- Khalil, M.D. Vanderbilt Univ. Med. Ctr. Department of Neurology 1161 21 St Ave. South A-0118 Med. Ctr. North Nashville, TN 37232 Site# 001	Protocol VRX- RET-E22-301- Number of subjects listed 20	4/26-30/10	Pending Preliminary: VAI
Ronald Aung-Din, M.D. Lovelace Scientific Resources 5741 Bee Ridge Road Sarasota, FL 34233 Site# 014	Protocol VRX- RET-E22-301 Number of subjects listed 14	7/12-15/10	Pending Preliminary: VAI
Christian E. Elger, M.D. Klinik und Polyklinik fur Epileptologie Sigmund-freud-Str.25 Bonn, NW 53127 Germany Site# 401	Protocol VRX- RET-E22-302 Number of subjects listed 38		Pending Preliminary: VAI
Sergiy Kharchuk, M.D. Epilepsy Ctr. Of Municipal Clinical Psychoneurological Hos. Epileptology Dept. Frunze Str.103-A Kiev 04080, Ukraine Site# 853	Protocol VRX- RET-E22-302 Number of subjects listed 24		Pending Preliminary: NAI
Valeant Pharmaceuticals Research America	Protocols E22-301 and 302	5/24-28/10	Pending

2512 South Tricenter Blvd. Research Triangle Park NC 27709 Sites# 001&853	Number of subjects listed 20 & 24		Preliminary: VAI
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Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Note: Observations noted below for all sites are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Protocol VRX-RET-E22-301

1. Bassell Abou Khalil, M.D.
Nashville, TN 37232

a. What Was Inspected: At this site, a total of 26 subjects were screened, 16 subjects were reported as screen failures (protocol allowed screen failures to be re-screened). For example, Subject #9 was also Subject #2 who was a screen failure. There were 22 different subjects (of the 26 screened). Four subjects were terminated for non-compliance and for adverse events which were documented. Sixteen (16) subjects were randomized and all 16 subjects completed the study and enrolled in the open-label study. There were no deaths and one subject was reported to have an SAE (post-ictal encephalopathy), which was reported to the sponsor but not in a timely manner to the IRB. Review of Informed consent documents for all records reviewed, verified that subjects signed prior to enrollment (exception noted below).

A review of the medical records/source documents was conducted. The medical records for all subjects were reviewed in depth, including drug accountability records, vital signs, laboratory test results, IRB records, use of concomitant medications; source documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

b. General observations/commentary: At the conclusion of the inspection, a 4 item Form FDA 483 was issued to Dr. Abou-Khalil. The medical records reviewed disclosed minor protocol violations and discrepancies between source documents and what was recorded in the case report forms. Our investigation found the following:

Protocol Violations:

- Subject # 01 did not have a diagnosis of epilepsy for 2 years or longer prior to enrollment.
- Subject #10 participated in an investigational drug study within 2 months of the screening Visit.
- Subject # 24 experienced post-ictal encephalopathy on 8/5/06 which was not reported to the IRB until 4/29/10.
- Subjects' study consent forms (7) were dated by site staff because the subjects on occasion had forgotten to write the date at the time the Subjects/representative's signature.

Record keeping violations:

- Subject# 9 seizure counts for 3 days were not recorded on the Partial Seizure Frequency Records section of the case report forms.
- Discrepancies were noted between the source documents and case report forms in that Subject #22 source documents and works sheets were discrepant for neurologic exam and gait and were inconsistent throughout the study.
- Subject #23 Visit 1 screening medical history and neurological exams reported abnormal diagnosis and findings; however, these were not reported for Visit 3.

The clinical investigator acknowledged the inspectional findings in which he stated in his written response dated May 18, 2010 that corrective action plans will be instituted and promised to exercise more care in his future studies.

c. **Assessment of Data Integrity:** Although regulatory violations were noted, the findings are unlikely to affect data integrity as they appear to be isolated occurrences and not systemic in nature. However, the review division may choose to consider the findings as outlined above with respect to protocol violations in their assessment of efficacy or safety. The remaining data generated from Dr. Khalil's site are considered reliable and appear acceptable in support of the application.

**2. Roland Aung-Din, M.D.
Sarasota, FL 34233**

a. What Was Inspected: At this site, a total of 17 subjects were screened, three (3) subjects reported as a screen failures were re-screened and 2 were accepted into the study. Fourteen (14) subjects were randomized and 7 subjects completed the study. There were no deaths and one under-reporting of adverse events (UTI). Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for 16 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, inclusion/exclusion criteria, and source documents were compared to data listings for primary efficacy endpoints and adverse events.

b. General Observations/Commentary: At the conclusion of the inspection, a two item Form FDA 483 was issued to Dr. Aung-Din. Our investigation found protocol violations and discrepancies in the types and number of seizures due to transcription errors and non-reporting of one adverse event.

Protocol Violations:

Two subjects, 01403 and 01416, were incorrectly instructed on how to take the study drug cards resulting in:

- Subject (01403) taking drug from card #6 prior to taking study drug from card # 5
- Subject 01416 received twice the amount of study drug for 5 days.

Three subjects were enrolled in the study who did not meet inclusion criteria.

- Subject 01411 had a QTC interval of 473 msec, which is greater than 430 msec allowed by the protocol.
- Subject 01414 had a documented history of drug abuse two days prior to screening and was being treated for an active infection.
- Subject 01412 had a documented history of one seizure per month 18 days prior to screening.
- Subject 01405 was randomized two weeks post screening rather than the four weeks specified by the protocol.
- 10 of 16 subjects had their blood drawn for genotyping done at Visit 2 rather than Visit 3 as specified by the protocol
- Two subjects, 01415 and 01416, were not consented with version 5 of the informed consent.
- Subject 01414 experienced urinary tract infection that was not reported to the sponsor.

Recordkeeping Violations:

- Subject 01416 experienced an altered Mental Status on (b) (6) and the IRB was not notified until 7/12/10

The medical records/source document reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. With the exception of items noted above, the records reviewed were found to be in order and verifiable and the data generated by this site appear acceptable in support of the respective indication. There were no known limitations to this inspection.

c. Assessment of Data Integrity

Although regulatory violations were noted, the findings are not likely to affect data integrity. However, the review division may choose to consider the isolated discrepancies noted above in their assessment of safety or efficacy. The remaining data from Dr. Aung-Din's site are considered reliable and appear acceptable in support of the pending application.

Protocol VRX-RET-E22-302

**3. Christian E. Elger, M.D.
Bonn, NW Germany**

a. What Was Inspected: At this site, a total of 43 subjects were screened, 4 subjects were reported as screen failures, 38 subjects were randomized into the study, 18 subjects were discontinued and 24 subjects completed the study. Two subjects withdrew from the study: Subject 202-07 (b) (6) (positive pregnancy after first dose) and Subject 558 (b) (6) (experienced generalized allergic rash). Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 10 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria use of concomitant medications; source documents for 12 subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events and no discrepancies were noted.

b. General Observations/Commentary: At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Elger. Our investigation found that 3 subjects were enrolled into the study contrary to protocol inclusion criteria.

- Subject 40141 was enrolled in the study with significant EKG abnormality with a QTC interval greater than 430 msec allowed by the protocol. The subject was later withdrawn from the trial with no clinical sequelae resulted from EKG abnormalities.
- Subject 40101 had a bladder tumor measuring 2.7 cm x 1.6 x 1.7 cm was randomized into the study in violation of the protocol inclusion criteria; the subject underwent a transurethral resection of the bladder and histology confirmed bladder carcinoma. An SAE was reported as "urethral carcinoma of the bladder."
- Subject 40113 did not have a screening EKG for the screening Visit. The subject was enrolled into the study prior to receiving and evaluating the laboratory result in order to confirm eligibility.

The clinical investigator acknowledged the inspectional findings in a written response dated March 25, 2010, in which he stated that corrective measures will be instituted and promised to exercise more care in his future studies. I find his response acceptable.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and the data verifiable. There were no known limitations to this inspection.

c. Assessment of Data Integrity: Although regulatory violations were noted, the findings are unlikely to affect data integrity. The review division may wish to exclude the three subjects from the final analyses. The remaining data generated from Dr. Elger's site are considered reliable and appear acceptable in support of the application.

**4. Sergiy Kharchuk, M.D.
Kiev, Ukraine**

- a. **What was Inspected:** At this site, a total of 26 subjects were screened, 2 subjects were reported as screen failures, 24 subjects were randomized and 19 subjects completed the study. Six (6) subjects withdrew from the study and the reasons were documented. Review of Informed Consent Documents, for all subjects reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source data for all subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, diary cards, IRB files, prior and current medications, inclusion/exclusion criteria, the use of concomitant medications; source documents for selected subjects were compared to case report forms and to data listings for primary efficacy endpoint and adverse events. No Form FDA 483 was issued.

- b. **General Observations/Commentary:** The medical records reviewed disclosed no adverse findings that would negatively on the reliability of the data. In general, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.
- c. **Assessment of Data Integrity:** The data from Dr. Kharchuk's site are considered reliable and appear acceptable in support of the pending application.

**5. Valeant Pharmaceuticals Research America.
Research Triangle Park, NC 027709**

- a. **What was Inspected:** The sponsor, Valeant Pharmaceuticals, inspection was conducted because Potiga (retigabine) is a New Molecular Entity. The inspection audited Protocols VRX-RET-E22-301 and #302 and focused on two clinical investigators. The field investigator and headquarter representative joined the EMA team to review the firm's various operating procedures (SOPs) in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program, including the monitoring SOPs.

- b. **General Observations/Commentary:** The inspection covered study data generated by two sites, one domestic and one foreign. In general, our field investigator found no significant objectionable conditions in terms of under-reporting of adverse events, adequate quality assurance system (QA) and adequate records. A Form FDA 483 was issued at the conclusion of the inspection for the failure to:
1. Provide the clinical investigators with information needed to conduct the study in terms of additional safety procedures requested by the agency.
 2. Obtain, retain and provide upon request information regarding curriculum vitae or statement of the qualifications of investigators and selection of monitors.
 3. Provide training documentation of staff involved in the study.
 4. Submit an addendum to the protocol instead of granting 34 waivers for subjects not meeting inclusion/exclusion criteria.
 5. Ensure adequate monitoring at certain sites.

The sponsor acknowledged the inspectional findings in a written response dated June 18, 2010, in which the sponsor promised to institute the following steps:

1. Maintain strict adherence to the protocol.
2. Ensure that should protocol waivers be considered or granted in the future an amendment to the protocol will be in place.
3. Ensure that clear guidance to the CRAs on reporting expectations.
4. Ensure monitoring for any trends across all sites that may require retraining of monitors, clinical investigators and /or site staff.
5. Will ensure that CRO standard procedures and requirements are consistent with the requirements as stated in the protocol.
6. Will maintain copies of CV's and training written materials on files for future studies.

The sponsor written response to the inspectional findings appears to be acceptable for being committed to resolve the related observations noted during the inspection.

The medical documents reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data.

- c. **Assessment of Data Integrity:** In general, the records and documents reviewed were found to be in order and verifiable. Although regulatory violations were noted as above, these do not appear systemic in nature and are unlikely to impact data reliability. The data generated appear to be acceptable in support of this application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four clinical investigators, two domestic and two foreign sites, and the sponsor were inspected in support of this application. The inspections of Drs. Khalil, Aung-Din, Elger, and Kharchuk revealed no significant problems that would adversely impact data acceptability. In addition, the sponsor inspection identified minor violations that are unlikely to impact data reliability. Overall the data submitted from these sites are acceptable in support of the pending application.

Note: Observations noted above for all inspections are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

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

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

/s/

ANTOINE N EL HAGE
08/09/2010

TEJASHRI S PUROHIT-SHETH
08/10/2010

Division of Reproductive and Urologic Products (DRUP)
Consultation re: Retigabine (Potiga) (NDA 22-345)

To: DNP

From: Chong Kim, MD, PhD (MO DRUP)
Mark Hirsch, MD (Team Leader, DRUP)
George Benson, MD (Deputy Director, DRUP)

Urologic considerations

Retigabine (RTG), N-[2-amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, is a first in class neuronal potassium (KCNQ) channel opener-potentiator proposed for the indication of treatment of partial-onset seizures. KCNQ genes encode a family of voltage-dependent ion channels that maintain cellular membrane potential, regulate neurotransmitter release, and control subthreshold electrical excitability in neurons.

Two urologic safety issues arose during the review of NDA 22-345:

- 1. Urinary retention and voiding dysfunction**
- 2. Urinary crystals and the potential for stone formation**

Urinary retention and voiding dysfunction

Relevant preclinical studies:

In addition to their expression in neurons, KCNQ channels are also found in vascular smooth muscle, urinary bladder, and intestine. RT-PCR revealed that KCNQ1, KCNQ3 and KCNQ5 are expressed in rat urinary bladder smooth muscle cells, with KCNQ5 being the most highly expressed. Retigabine (RTG) hyperpolarized the resting membrane potential in isolated rat bladder smooth muscle cells and increased outward K⁺ current.

Consistent with these in vitro observations, in the hypertrophied bladder model RTG decreased the frequency of spontaneous bladder contractions, while in the neurogenic bladder model RTG blocked micturition in a dose-dependent manner. Various urinary bladder effects including distension and associated effects in kidneys have been observed in mouse, rat, and dog toxicity studies. In 14-day oral gavage mouse repeat-dose toxicity studies, macroscopic observations included a distended abdomen, focal lesions of the penis, and hematuria. Fluid in the abdominal cavity, seen in early decedent animals with higher doses of RTG, was presumed to be a result of bladder perforation. In addition, a thickened bladder wall and bladder calculi were seen in RTG-treated mice. Further observations at necropsy included dilatation of ureters, discolored renal cortices, and renal pelvic dilatation. The urinary system toxicities elicited by RTG were sufficiently marked as to be considered unlikely to allow a sufficient rate of long-term survival of study animals.

Clinical studies:

Outline of Primary Placebo-Controlled, Safety-Efficacy Studies 205, 301, and 302

	Study 205	Study 301	Study 302
Phase/Sponsor	IIb/Wyeth	III/Valeant	III/Valeant
Treatment Group	600, 900, 1200 mg/day, PBO	1200 mg/day, PBO	600, 900 mg/day, PBO
Dosage Forms Used	50 mg, 100 mg or 200 mg IR capsules (note: 600 mg dose = 2X100 mg capsule TID; 900 mg dose = 3X100 mg capsule TID; 1200 mg dose = 1X 200 mg and 2X 100 mg capsule TID)	50 mg, 100 mg, 300 mg IR tablets (note: 1200 mg dose = 1X 300 mg tablet and 2X 50 mg tablets TID)	50 mg and 100 mg IR tablets (note: 300 mg dose = 3X 100 mg tablets TID)
Duration of Double-blind	16 weeks	18 weeks	16 weeks
Duration of Titration	8 weeks	6 weeks	4 weeks
Duration of Maintenance	8 weeks	12 weeks	12 weeks
Countries	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland Portugal ,Slovakia, Spain, Sweden, UK, and US	Argentina, Brazil Canada, Mexico, and US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, S Africa, Spain, UK Ukraine, and US

Trial 205:

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, **dose-ranging study**.

Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
N = 96	N=100	N= 95	N = 106

Trial 301:

This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group **phase 3 study**.

Placebo	RTG 1200 mg/day
N=152	N=153

Trial 302:

This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group **phase 3 study**.

Placebo	RTG 600 mg/day	RTG 900 mg/day
N=179	N=181	N=178

Urinary retention and lower urinary tract dysfunction in placebo-controlled trials:

In Trial 205:

- Subjects with urogenital system treatment emergent adverse events reported during the double blind phase of Trial 205 (titration and maintenance periods)

Coded term	Number (%) of patients			
	Placebo (N = 96)	Retigabine		
		200 mg TID (N = 100)	300 mg TID (N = 95)	400 mg TID (N = 106)
Urine abnormality	0	4 (4.0)	3 (3.2)	4 (3.8)
Hematuria	1 (1.0)	1 (1.0)	2 (2.1)	2 (1.9)
Urinary tract infection	3 (3.1)	2 (2.0)	3 (3.2)	2 (1.9)
Urinary frequency	0	0	1 (1.1)	2 (1.9)
Dysuria	0	0	0	2 (1.9)
Urination impaired	0	0	3 (3.2)	1 (0.9)
Kidney pain	1 (1.0)	0	2 (2.1)	1 (0.9)
Impotence	0	1 (1.0)	1 (1.1)	1 (0.9)
Cystitis	0	0	0	1 (0.9)
Prostatic disorder	0	0	0	1 (0.9)
Fibrocystic breast	0	0	0	1 (0.9)
Menopause	0	0	0	1 (0.9)
Albuminuria	0	1 (1.0)	0	0
Epididymitis	1 (1.0)	1 (1.0)	0	0
Kidney failure	0	1 (1.0)	0	0
Ovarian disorder	0	1 (1.0)	0	0
Oliguria	0	1 (1.0)	0	0
Urinary urgency	0	1 (1.0)	0	0
Dysmenorrhea	2 (2.1)	0	0	0
Amenorrhea	1 (1.0)	0	0	0
Ovarian cyst	1 (1.0)	0	0	0
Vaginitis	1 (1.0)	0	0	0
Presented in order of decreasing frequency in the retigabine 400 mg TID group. Note that the scheduled dose might not have been reached at the time of the occurrence of the event. Source: Table V 5.3 (Section 14.3.1)				

- Preferred adverse event (AE) terms encompassing voiding dysfunction were all considered mild to moderate in severity. One patient (Number 0448) with the preferred AE term of “kidney failure due to urinary retention” was discontinued from study medication:

Patient 0448 in the 200mg TID RTG group experienced renal failure due to urinary retention. This 53 year-old female started therapy on April 5, 2000, and the AE occurred on (b) (6) following 19 days of receiving RTG. She was hospitalized and noted to have a post-catheterization residual urinary volume of 1500cc, serum creatinine of 4.5 mg/dL, and hydronephrosis. Study medication was discontinued on May 7, 2000. Renal and voiding function normalized after a period of post-obstructive diuresis. This subject with a preferred term AE of kidney failure was also counted as a urinary retention AE.

- The AE of “impaired urination” in Study 205 occurred in 4/301 retigabine treated patients versus 0/96 placebo patients.

In Trial 301:

- The incidences of AEs for renal and urinary disorders for patients in the retigabine group were 23% versus 7% for the placebo group. More patients in the retigabine group versus the placebo group reported AEs in the preferred term categories of urinary tract infection (12% vs 9%), urinary hesitation (5.9% vs 0.7%), and dysuria (5.2% vs 1.3%).
- All adverse events related to voiding dysfunction were mild or moderate in severity. During the double-blind phase, there were no serious AE’s due to voiding dysfunction, and no dose reductions nor discontinuations due to voiding dysfunction in the retigabine group.

Study 301: Renal and Urinary Disorder Adverse Events Reported by 2 or More Patients in Either Treatment Group During the Double-blind Phase (titration and maintenance periods)

System organ class	Number (%) of patients	
	Placebo (N=152)	RTG 400 mg TID ^a (N=153)
Any renal and urinary disorder adverse event	10 (6.6)	35 (22.9)
Urinary hesitation	1 (0.7)	9 (5.9)
Dysuria	2 (1.3)	8 (5.2)
Chromaturia	0	7 (4.6)
Polyuria	1 (0.7)	4 (2.6)
Nephrolithiasis	0	4 (2.6)
Haematuria	1 (0.7)	2 (1.3)
Urinary retention	2 (1.3)	1 (0.7)

^a Adverse events are presented in descending order of incidence in the retigabine group.
RTG = retigabine, TID = three times daily

- Patient 02508 in the 400 mg tid retigabine treatment group had a preferred term AE of urinary retention which did not require any intervention. Mild clinical symptoms of urinary retention resolved and the patient continued treatment with retigabine.

- Patients 05203 and 20217, randomized to placebo, both reported an episode of urinary retention during the double blind-treatment phase.

The finding in Study 301 of an increased incidence of mild to moderate urinary hesitation and dysuria in the retigabine treated group compared to the placebo group is consistent with the finding of drug-related “impaired urination” in Study 205. In Study 301, however, cases of “urinary retention” occurred in only one RTG patient and two placebo patients.

In Study 302:

- Five adverse events of urinary retention (1.4%) were reported in the retigabine treatment groups versus none in the placebo group. Urinary tract infection was reported in 1.7% of placebo treated patients, 1.7% of 600 mg retigabine treated patients, and in 2.8% of 900 mg retigabine treated patients.

Study 302: Renal and Urinary Disorder Adverse Events Reported by 2 or More Patients in Any Treatment Group During the Double-blind Phase – Safety Population

System organ class	Number (%) of patients		
	Placebo (N=179)	RTG 200 mg TID (N=181)	RTG 300 mg TID (N=178)
Any renal and urinary disorder event	14 (7.8)	23 (12.7)	15 (8.4)
Dysuria	0	3 (1.7)	4 (2.2)
Urinary retention	0	1 (0.6)	4 (2.2)
Haematuria	2 (1.1)	5 (2.8)	2 (1.1)
Polyuria	4 (2.2)	1 (0.6)	2 (1.1)
Chromaturia	1 (0.6)	1 (0.6)	2 (1.1)
Urinary hesitation	3 (1.7)	6 (3.3)	1 (0.6)
Proteinuria	3 (1.7)	2 (1.1)	0
Leukocyturia	2 (1.1)	2 (1.1)	0
Micturition frequency decreased	1 (0.6)	2 (1.1)	0
Urine flow decreased	2 (1.1)	1 (0.6)	0
Crystalluria	0	2 (1.1)	0

Adverse events are presented in descending order of incidence in the retigabine 300 mg TID group.

RTG = retigabine.

Source: [Table 12.2.9.1](#) (Section 14.3.1)

- 14 female and 8 male patients listed below had voiding dysfunction listed in the renal and urinary disorders System/Organ/Class (SOC) during the double blind treatment phase. All but two of the cases were considered mild or moderate in severity. There were no dose reductions for voiding dysfunction. Two patients had discontinuation of retigabine study medication for voiding dysfunction during the double-blind study period.

Study 302: Details of Adverse Events Related to Urinary Retention by Study Phase

Patient number	Preferred term	Start Day (Duration)	PVR (mL) at BL, W8, W16, Term	Severity	Action ^a	Related	SAE
Retigabine 300 mg TID (900 mg/day) – double-blind phase							
25108	Urinary retention	19 (39)	0, 1, 2, --	Mild	None	Possible	Yes
25215	Urinary retention	56 (Ongoing)	30, 156, 83, --	Mild	None	Possible	No
25405	Atonic urinary bladder	21 (140)	29, 159, 83, --	Moderate	Disc	Probable	Yes
30301	Urinary retention	29 (14)	38, --, --, 101	Severe	Disc	Probable	No
40119	Residual urine volume	114 (Ongoing)	115, --, 246, --	Mild	None	Possible	No
40701	Residual urine volume	58 (57)	31, 150, 40, --	Moderate	None	Possible	No
50102	Residual urine volume	57 (Ongoing)	7, 60, 180, --	Severe	None	Possible	No
50606	Residual urine volume	35 (Ongoing)	11, --, --, 65	Mild	None	Not related	No
60214	Urinary retention	32 (Ongoing)	30, --, --, --	Mild	None	Probable	No
80404	Urinary hesitation	33 (1)	140, 25, 55, --	Mild	None	Possible	No

Retigabine 200 mg TID (600 mg/day)– double-blind phase							
25407	Urinary retention	41 (44)	33, 28, 7, --	Mild	None	Possible	No
25411	Urinary hesitation	25 (33 – 64)	32, --, --, 10	Mild	None	Possible	No
40602	Micturition disorder	15 (Ongoing)	6, 15, 25, --	Mild	None	Possible	No
60210	Urinary hesitation	16 (95)	16, 12, 0, --	Mild	None	Probable	No
60215	Urinary hesitation	89 (38)	0, --, --, --	Mild	None	Probable	No
	Micturition freq decr	89 (38)		Mild	None	Probable	No
60402	Urinary hesitation	21 (3)	5, 9, 0, 10 ^b	Mild	None	Possible	No
	Urinary hesitation	51 (3)		Mild	None	Possible	No
60410	Urine flow decreased	14 (16)	0, --, --, 0	Mild	None	Possible	No
60501	Micturition freq decr	10 (32)	15, --, --, 33	Mild	None	Possible	No
60510	Urinary hesitation	53 (19)	25, --, --, 48, --	Mild	None	Possible	No
60601	Hypertonic bladder	49 (72)	7, 143, 0, --	Mild	None	Possible	No
60604	Bladder disorder	56 (Ongoing)	0, 88, 270, --	Mild	None	Possible	No
80304	Urinary hesitation	27 (Ongoing)	120, 660, --, --	Mild	None	Probable	No

- Two renal and urinary disorder AEs were reported as serious adverse events (SAEs).

Patient 25108, a 31 year-old female, had clinical complaints of voiding dysfunction on day 19 of the titration phase on retigabine 300 mg TID. Post-void residual (PVR) urines at various times were minimal and the patient continued in the study with resolution of symptoms.

Patient 25405, a 34 year-old female, had voiding dysfunction with PVR's of 159 and 83cc. She was discontinued from the study with resolution of her voiding dysfunction.

- Two additional patients had severe AEs in the SOC of renal and urinary disorders.

Patient 30301 had a preferred term AE of urinary retention. The patient was a 47 year-old female randomized to retigabine 300 mg TID on October 18, 2006. On November 15, 2006, (day 29 of treatment) she reported severe symptoms of straining to urinate and began tapering off of study drug. Her PVR at that time was 101 cc.

Patient 50102, a 47 year-old female, had a preferred term AE of “residual urine volume.” She began treatment on June 22, 2006, with a baseline PVR of 7 ml. On August 17, 2006, she had a PVR of 60 ml, on October 11, 2006, a PVR of 180 ml, and on December 6, 2006, a PVR of 200 ml. She had no complaints of voiding dysfunction and continued in the study.

- Three additional patients had ongoing AEs related to increased PVRs.

Patient 40119, a 57 year-old female, began taking retigabine on December 19, 2006. Her baseline PVR was 115 ml. While on retigabine 900 mg/day, on April 11, 2007, she had complaints of voiding dysfunction and was noted to have a PVR of 246 ml. There was no dose modification and patient continued in the study.

Patient 60604, an 18 year-old female, began taking retigabine on July 18, 2006. Her baseline PVR was 0 ml. On November 8, 2006, she was noted to have a PVR of 270 ml. She had no complaints of voiding dysfunction. She continued in the study without dose reduction and completed the study. She took the last dose of study medication on March 5, 2007, and the last PVR performed on June 8, 2007, was 8 ml.

Patient 80304, a 56 year-old male, began taking retigabine on September 1, 2006. His baseline PVR was 120 ml. He reported voiding dysfunction on September 27, 2006, and a PVR of 660 ml was noted on October 12, 2006. A PVR on May 10, 2007, was 375 ml. He had persistent voiding dysfunction but remained on retigabine 600 mg/day and completed the study.

The finding of urinary retention and urinary hesitation reported as AEs in a greater percentage of retigabine patients versus placebo patients was observed again in Study 302. Most of the reported cases of “voiding dysfunction” in the retigabine treated group in this study were mild or moderate in severity. There were only 2 cases that led to study drug discontinuation, two coded as SAEs, and two cases rated as severe. There does not appear to be a clear correlation between increased post-void residual urine and reported symptoms.

In Study VRX-RET-E22-303 (Open label extension of Trial 301)

- Trial 303 is an open-label long-term extension of Study 301. Patients who completed the transition phase of Study 301 were to begin the open-label extension at a target dose of 1200 mg/day on the day following eligibility assessment. Patients who did not tolerate their final dose during the transition phase could begin the open-label extension at a lower dose of retigabine. During Study 303, the investigator could modify the dose of retigabine to optimize patient response and tolerance.

- Interim data were submitted with a median time on open-label treatment for all patients of 357 days.
- 12% of patients had AEs reported in the SOC of renal and urinary disorders. Four (2.2%) subjects had the preferred term AE of urinary retention that was rated as mild, 3 (1.7%) patients had urinary retention that was rated as moderate, and 1 (0.6%) patient had urinary retention that was rated as severe and required study discontinuation.

Trial 303. Renal and Urinary Disorder Treatment-Emergent Adverse
Events Reported by Two or More Patients During the Open-
Label Extension Period

Preferred term ^a	Number (%) of Patients (N=181)	
Any renal and urinary disorder adverse event	22	(12.2)
Urinary retention	8	(4.4)
Dysuria	4	(2.2)
Urinary hesitation	3	(1.7)
Bladder spasm	2	(1.1)
Nephrolithiasis	2	(1.1)
Pollakiuria	2	(1.1)
Urinary incontinence	2	(1.1)

^a Adverse events are presented in descending order of incidence.

Source: [Table 15](#) (Section 14.3.1)

- Case narratives of four patients with the SAE of urinary retention are presented:

Patient 00103, a 21 year-old female, experienced an SAE which required hospitalization on (b) (6). The hospital admission was precipitated by seizures, confusion, fever, and UTI. Overall, this patient's renal and urinary SAEs consist of voiding dysfunction, UTI, hematuria, and hydronephrosis.

Patient 00902, was a 39 year-old male who had initially been randomized to the 400 mg TID RTG group on April 6, 2006, and began treatment in the open-label extension study on September 20, 2006. He required hospitalization on (b) (6), for postictal psychosis and urinary retention while on a retigabine dose of 300 mg TID. On (b) (6) of treatment), a urology consultation was obtained and a bladder ultrasound revealed a PVR urine volume of 700 cc and a urinary catheter was placed. This urinary retention episode was reported to be resolved on March 11, 2008 (day 706). On (b) (6), he was admitted to the hospital because of seizures and urinary retention. The patient was catheterized on (b) (6) and 990 cc of urine obtained and the patient was started on tamsulosin 0.4 mg. This episode of urinary retention was reported to be resolved August 27, 2008, and patient remained in the study on treatment.

Patient 3505, a 30 year-old male, who had initially been randomized to placebo began retigabine open label treatment on January 9, 2008, at 400 mg TID. On (b) (6) of RTG treatment), he was seen in the emergency room and admitted to the hospital for observation because of psychomotor agitation, urinary retention, and upper respiratory infection. A urinary catheter was inserted and 1200 cc of urine was evacuated. Study drug was reduced to 1050 mg/day on January 23, 2008 (Day 55), and discontinued on February 20, 2008 (day 83). At some point he had been placed on self-intermittent catheterization. At a follow-up visit to the urology clinic on May 5, 2008 (day 158), he reported improvement and a PVR in the office revealed 91 cc of residual urine. On June 3, 2008 (day 187), he reported improved symptoms and the ability to spontaneously void and was self catheterizing less frequently.

Patient 03901 was a 58 year-old male who was in the placebo group in Study 301. He experienced the SAE of urinary retention during the transition period onto retigabine treatment for the open label extension study. On June 12, 2007, he began transition to retigabine. He experienced severe oliguria beginning June 28, 2007, and mild abdominal pain on July 2, 2007. On July 9, 2007, he was taking retigabine 250 mg TID and an interim PVR ultrasound revealed a pre-void urine volume of 2187 mL and a post-void residual of 572 mL. He was discontinued from retigabine treatment on July 13, 2007. On July 16, 2007, three days after his last dose of study drug, the patient's pre-void volume was 162 mL and a post-void residual volume of 0 mL. During a follow-up phone call on August 13, 2007, the patient reported no urinary complaints.

Summary of Lower Urinary Tract Adverse Events in Primary Placebo-Controlled Safety-Efficacy Studies

The overall incidence of voiding dysfunction related AEs, which may represent impaired bladder contractility, was 3.8 % in the retigabine group verses 1.4 % in the placebo group in the three placebo controlled studies. The incidence of urinary retention was 0.9 % for the retigabine treatment group versus 0.4 % for the placebo treatment group.

	Placebo N=427	RTG N=813
Urinary retention	2 (0.4%)	7 (0.9%)
Urinary hesitation	4	16
Atonic urinary bladder	0	1
Urination impaired	0	4
Urinary frequency	0	3
	6/427 (1.4%)	31/813 (3.8%)

If the four additional cases of urinary retention in the open label extension study are added to the RTG group, the incidence of urinary retention with RTG is 1.4 %.

Although the number of patients with voiding AE's is relatively small, the incidence of voiding dysfunction may be dose related (see table below). There were no dose reductions due to voiding dysfunction during the trials.

	Placebo N=427	600 mg N=281	900 mg N=273	1200 mg N=259
Urinary retention	2	2	4	1
Urination impaired	0	0	3	1
Urinary hesitation	4	6	1	9
Atonic urinary bladder	0	0	1	0
Urinary frequency	0	0	1	2
	6/427	8/281	10/273	13/259
	1.4%	2.9%	3.6%	5.0%

DRUP Conclusions and Comments Relating to Lower Urinary Tract Dysfunction:

1. Retigabine therapy is associated with an increased risk of voiding dysfunction, including urinary retention.
2. Several of the patients experienced urinary retention within the first month of therapy with retigabine, but others had been on the drug for many months.
3. The incidence of urinary retention in the placebo controlled studies is higher than that seen in placebo controlled trials of anticholinergic drugs for the treatment of overactive bladder.
4. Based on pre-clinical studies, the investigators were aware of potential bladder effects of retigabine. In Study 301, all patients had a post-void residual urine determined at baseline and again at weeks 10 and 18 of the maintenance phase. In Study 302, all patients had a post-void residual urine determined at baseline and at weeks 8 and 16 of the maintenance phase. Urinary retention occurred despite awareness of this adverse event and post-void residual measurements. It is possible, but unlikely, that more frequent and earlier post-void residual measurement could have lessened the incidence of urinary retention.

5. In the submitted draft labeling, the sponsor has placed (b) (4) as the first Warning and Precaution included on the Highlights Page. In addition, (b) (4) is stated in the Warnings and Precautions (section 5.1) of the label. The sponsor also proposes a Medication Guide which includes information on lower urinary tract dysfunction. Finally, the sponsor proposes a prospective epidemiologic study to further assess the risk of urinary retention. DRUP believes that, if substantial efficacy is demonstrated, the safety issue of lower urinary tract dysfunction including urinary retention can be adequately managed by the sponsor's proposals.

Urinary crystals and the potential for stone formation:

In vitro studies:

Retigabine is not soluble in an aqueous solution of 0.1 N NaCl nor in an aqueous solution of normal physiological range of urine pH. Retigabine is mainly eliminated through the renal route, as evidenced by 84% of total radioactivity recovered in the urine, with unchanged parent compound in the urine accounting for 36% of the administered dose.

pH Solubility Profile of Retigabine in Aqueous Media at 37°C

Solution pH at 37°C	Solubility of Retigabine in g/L

Mass spectrometry of urine identified peaks corresponding to the known molecular weights of retigabine and retigabine dimers.

Study 205:

The proportion of patients with amorphous sediment in the urine (urinalysis) tended to increase with increasing retigabine dose during the titration and maintenance phases. At the end of the maintenance period, the proportion of patients with values for this parameter were 52% for placebo, 73% for 200 mg TID, 69% for 300 mg TID, and 84% for 400 mg TID.

One patient in study 205 experienced renal colic due to urolithiasis (Patient 0125 in the RTG 300 mg TID group). This 39 year-old male started therapy on November 24, 1999, and this AE began on (b) (6) of treatment). During participation in the retigabine protocol, the patient was noted to have back pain and left hydronephrosis due to an obstructing distal ureteral calculus. His urolithiasis was surgically treated and the stone fragment identified as calcium oxalate monohydrate. The sponsor was contacted to determine if the stone fragment were available for further analysis, specifically looking for retigabine. The stone fragment was not available for further analysis.

Study 301:

The proportion of patients with urinary sediment / crystals at the end of maintenance period in Study 301:

Parameter	Placebo	Retigabine 1200 mg/day
Amorphous crystals	0/119	3/87 (3.4%)
Amorphous phosphates	1/119 (0.8%)	1/87 (1.1%)
Amorphous urates	7/119 (5.9%)	12/87 (13.8%)
Calcium oxalate crystals	4/119 (3.4%)	6/87 (6.9%)
Uric acid crystals	2/119 (1.7%)	7/87 (8%)
pH (mean; change from baseline)	5.88 ; -0.08	5.67 ; -0.23

- Four patients had reported AEs of nephrolithiasis in the retigabine treatment group versus none in the placebo group.

Subject 00302, a 32 year-old male, began taking blinded retigabine on June 3, 2006, and reached maintenance phase of the study on July 20, 2006. While on retigabine 950 mg/day, he reported passing a kidney stone on September 6, 2006. The event was assessed as resolved on the same day and the patient continued in the study.

Subject 00901, a 38 year-old male with a history of urolithiasis, began taking retigabine on January 5, 2006, and entered the maintenance phase on February 15, 2006. While on retigabine 1050 mg/day, he reported back pain on February 25, 2006, and was diagnosed with “kidney stones” on March 1, 2006. The event was reported as resolved on April 12, 2006, and the patient continued in the study.

Subject 20210, a 37 year-old female, began taking retigabine on December 2, 2006. On January 13, 2007 (day 43), she discontinued study medication due to CNS related AEs. At the final study visit on January 19, 2007, she reported “renal lithiasis” of mild intensity.

Subject 20221, a 36 year-old male, began taking retigabine on June 12, 2007, and entered the maintenance phase on July 23, 2007. While on retigabine 1200 mg/day, he reported mild “nephric lithiasis” on August 20, 2007. He continued in the study without interruption and the event resolved on October 15, 2007.

Study 302:

The proportion of patients with urinary sediment / crystals at the end of maintenance period in Study 302

<u>parameter</u>	<u>placebo</u>	<u>600 mg/day</u>	<u>900 mg/day</u>
Amorphous crystals	18/141 (12.8%)	24/126 (19%)	30/116 (25.9%)
Amorphous phosphates	1/141 (0.7%)	0/126 (0%)	1/116 (0.9%)
Amorphous urates	6/141 (4.3%)	5/126 (4%)	8/116 (6.9%)
Calcium oxalate crystals	8/141 (5.7%)	7/126 (5.6%)	11/116 (9.5%)
Uric acid crystals	1/141 (0.7%)	7/126 (5.6%)	2/126 (1.7%)
pH (mean; change from baseline)	5.83 ; -0.16	5.74 ; -0.14	5.63 ; -0.23

- No AEs of nephrolithiasis were reported in Study 302.

Summary of Urinary Crystals and the Potential for Stone Formation in Placebo-Controlled Safety-Efficacy Studies

“Nephrolithiasis” was reported in five patients, representing 0.6% of the retigabine treated safety population (see table below). “Kidney pain” and “hematuria” were also reported more frequently in patients in the retigabine group compared to the placebo group.

	Placebo N=427	RTG N=813
Kidney failure	0	1 (0.1%)
Urinary tract infection	19 (4.4%)	33 (4.1%)
Nephrolithiasis	0 (0.0%)	5 (0.6%)
Kidney pain	1 (0.2%)	3 (0.4%)
Hematuria	4 (0.9%)	14 (1.7%)

DRUP Conclusions and Comments Relating to Urinary Crystals and the Potential for Stone Formation:

1. The incidence of “amorphous crystals” varied widely (from 3% to 84%) in the three placebo controlled trials. Two of the three trials did show an increase in the number of patients with “amorphous crystals” with increasing doses of RTG. It is not known whether or not any of the crystals are composed of retigabine or retigabine dimers.
2. Except for the one case where a stone composed of calcium oxalate was surgically removed, the cases of “nephrolithiasis” are poorly documented. No stones composed of retigabine or retigabine dimers have been identified.
3. Although the potential for formation of retigabine stones exists, there is no clear clinical evidence implicating retigabine in urinary tract stone formation.

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

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

/s/

MARK S HIRSCH

07/08/2010

Entered into DARRTS for Dr. Kim, who is on leave. I concur with this consult addendum.

GEORGE S BENSON

07/09/2010

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: June 30, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Evaluation of Abuse Potential of Ezogabine (Potiga)
NDA 22-345
Indication: Adjunct Treatment of Partial-Onset Seizures
(200-400 mg TID; 600-1200 mg/day)
Sponsor: Valeant Pharmaceuticals, North America
PDUFA Goal Date: August 30, 2010
Advisory Committee Date: August 11, 2010

I. Executive Summary

A. Background

This memorandum summarizes the findings related to the CSS abuse potential assessment of ezogabine and provides recommendations to the Division of Neurology Products.

Ezogabine is a new molecular entity that is not currently marketed in any country. It is the first potassium channel opener to be evaluated by FDA for abuse potential.

CSS review of the abuse-related clinical and preclinical data in the NDA shows that:

1. Ezogabine is a central nervous system depressant. In rat and monkey toxicity studies, high doses of ezogabine produce a reduction in locomotor behavior, a reduction in muscle tone and ataxia, similar to that of a sedative-hypnotic. Further increases in dose produce seizures and death.

2. The mechanism of action of ezogabine appears to be through its ability to open neuronal KCNQ potassium channels, with an additional contribution through GABA-mediated neurotransmission. Ezogabine does not have binding affinity to any CNS site typically associated with abuse potential. The major metabolite, N-acetyl-retigabine, was not tested in electrophysiological or binding studies to determine its mechanism of action.
3. In rats trained to self-administer the Schedule II stimulant, cocaine, substitution of ezogabine did not maintain self-administration.
4. Phase 1 clinical pharmacokinetic studies have identified two primary routes of metabolism for ezogabine: N-acetylation and glucuronidation. In humans, the major circulating metabolite of ezogabine is N-acetyl-retigabine. The T_{max} of ezogabine ranges from 1-4 hours while the T_{max} of N-acetyl-retigabine ranges from 2-3 hours. Both compounds produce dose-proportional C_{max} values and have half-lives ranging from 6-10 hours.
5. In 21 Phase 1 pharmacokinetic, tolerance and safety clinical studies with ezogabine (200 to 1650 mg, p.o.) in healthy individuals (n = 469), there was a high incidence of euphoria and feeling drunk (5.5% to 8.5%), as well as reports of hallucination, disorientation and feeling abnormal (1.5% to 1.7%). Similarly, in a Phase 1 human abuse potential study with ezogabine (300 to 900 mg, p.o.) in healthy sedative-hypnotic recreational abusers (n = 26), there was a high incidence of euphoria (18% to 33%).
6. In three Phase 2/3 clinical efficacy studies that made up the Pivotal Clinical Trial database with ezogabine (300 to 1200 mg/day, p.o.) in patients with epileptic conditions who were concomitantly taking other antiepileptic and psychoactive drugs (n = 813), there was a low incidence of euphoria, feeling drunk and feeling abnormal (0.1% to 0.9%) compared to Phase 1 clinical studies. There were also reports of hallucination and disorientation (1.0% to 1.7%).
7. In a human abuse potential study (Study #VRX-RET-E22-108) in sedative-hypnotic recreational abusers (n = 26), ezogabine (300 and 600 mg, p.o.) produces positive subjective responses statistically similar to those produced by the Schedule IV sedative-hypnotic, alprazolam (1.5 and 3.0 mg, p.o.). Additionally, ezogabine produces negative subjective and cognitive responses that are statistically less than or similar to those produced by alprazolam. A 900 mg dose of ezogabine produced positive subjective responses that were greater than those produced by lower doses of ezogabine or alprazolam. The 900 mg dose also produced serious cardiac-related adverse events in two of six subjects who received the dose, including a case of nonfatal, spontaneously resolving asystole reported as a cardiac arrest and a case of nonfatal ventricular tachycardia.
8. In a human drug interaction study (n = 17), ezogabine (200 mg, p.o.) did not potentiate the ability of ethanol (1.0 g/kg, p.o.) to increase ratings on subjective scales of impairment, increase impairment on balance performance or increase impairment on

cognitive tests, compared to ethanol alone (1.0 g/kg). In contrast, 200 mg ezogabine alone did not induce impairment on these measures. Pharmacokinetically, ethanol only slightly increased the Cmax and AUC (0-8 hr) of ezogabine compared to ezogabine alone, but, conversely, ezogabine did not alter the pharmacokinetics of ethanol.

9. In Phase 2/3 clinical efficacy studies, ezogabine produces signs of withdrawal indicative of physical dependence. Abrupt discontinuation of ezogabine produced adverse events that included tremor, confusional state, psychotic disorder, dizziness, somnolence, vertigo, abnormal coordination, aphasia, dyspepsia, visual hallucination and myalgia, at a rate ranging from 1.4% to 5.1%. Tapered discontinuation of ezogabine also led to adverse events that included headache, dizziness, nausea, abdominal pain, diarrhea, influenza-like symptoms, disturbed attention, hematuria and depression at a rate ranging from 1.7% to 6.9%. A physical dependence study conducted in rats with ezogabine was inconclusive because no primary data were submitted for evaluation.

B. Conclusions

After a review of all abuse-related data submitted in the NDA, CSS has concluded that ezogabine is a central nervous system depressant that has an abuse potential similar to drugs in Schedule (b) (4) of the Controlled Substances Act (CSA).

This conclusion is based on similarity in abuse potential between ezogabine and (b) (4) drugs, (b) (4), with similar pharmacological effects that were recently placed into Schedule (b) (4). In separately-conducted human abuse potential studies, ezogabine, pregabalin and lacosamide each produce positive subjective effects that are statistically similar to those produced by a Schedule IV benzodiazepine (diazepam or alprazolam) positive control. Ezogabine, pregabalin and lacosamide also produce high rates of euphoria and other abuse-related adverse events in Phase 1 studies with healthy individuals. Additionally, ezogabine, pregabalin and lacosamide differ from diazepam and alprazolam in terms of their negative subjective response profile (on “Bad Drug Effects” and “Sedation” measures), pharmacokinetics, cognitive impairment and withdrawal syndromes following drug discontinuation. Thus, despite some similarities between ezogabine and the Schedule IV drug, alprazolam, ezogabine is most similar to the Schedule (b) (4) drugs, (b) (4), in terms of its overall abuse potential.

In the NDA, the Sponsor suggests that ezogabine has similar abuse potential to levetiracetam, an unscheduled medication marketed in the U.S. that was used as a “negative control” in the human abuse potential study. Thus, consideration was given to whether this is a valid conclusion. In the human abuse potential study, ezogabine and levetiracetam produced similar positive and negative abuse-related signals in recreational sedative abusers. These results with levetiracetam are similar to published reports showing that the drug can produce abuse-related subjective responses (Feltner and Haig, 2010; Wade et al., 2010). However, justification for the use of levetiracetam as a “negative control” is not scientifically valid because (b) (4)

Additionally, in the human abuse potential

study, the highest dose of ezogabine produced serious safety concerns that were not observed with levetiracetam. The 900 mg dose of ezogabine, which is slightly greater than twice the highest single therapeutic dose of 400 mg and 75% of the highest daily dose of 1200 mg, produced two serious cardiac adverse events, including a nonfatal, spontaneously resolving asystole reported as a cardiac arrest and a case of nonfatal ventricular tachycardia. Consideration of the risk to public health is Factor 6 in the Department of Health and Human Services' Eight Factor Analysis, which is required in the assessment of a drug's abuse potential and need for scheduling under the CSA (21 USC 811(b)). Thus, if ezogabine were marketed as an unscheduled drug, abuse of ezogabine at the 900 mg euphorogenic dose could produce serious outcomes.

(b) (4)

C. Recommendations (to be conveyed to Sponsor):

After a review of the materials submitted in the NDA, we recommend the following:

1. Ezogabine will be recommended for placement by DEA into Schedule ^(b)₍₄₎ of the Controlled Substances Act.
2. You should commit to report to FDA all cases of abuse, misuse, overdose and addiction associated with ezogabine after its introduction on the market.
3. You should 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 (e.g., serious cardiac adverse events at the 900 mg dose).

II. Summary and Discussion of Ezogabine Data Related to Abuse Potential

A. Preclinical Data Related to Abuse Potential

i. Electrophysiological Studies and Receptor Binding Studies

a. Electrophysiological Studies with Ezogabine (Study #D23129-FP10500, FP10100, FP10400, FP3095, FP10300, FP1295)

In six electrophysiological studies, ezogabine enhances currents mediated by four potassium KCNQ channel subtypes (2, 3, 4, 5), as well as currents mediated by neuronal KCNQ2/3 channels, in a concentration-dependent manner.

Ezogabine also acts less potently as a positive allosteric modulator of GABA-induced currents, in a concentration-dependent manner. This effect does not involve the benzodiazepine site of the GABA receptor-channel complex, since it is not inhibited by the benzodiazepine receptor antagonist, flumazenil. Published studies suggest ezogabine interacts with a novel site on the GABA_A receptor complex that is allosterically coupled with the binding sites for the agonist GABA and Org 20549 (a neuroactive steroid) ^{(b) (4)} [REDACTED]). Overall, these data suggest that ezogabine may modulate GABAergic neurotransmission, but this activity is likely to be secondary to the enhancement of current at potassium channels.

b. Receptor Binding Studies with Ezogabine (Study #D23129-FB4295)

In receptor binding studies, ezogabine (10^{-9} to 10^{-5} M) did not show significant interaction (percent inhibition < 50% at 10^{-5} M) at any of the 62 receptors, ion channels, transporters, enzymes, and second messengers tested, including the following CNS sites associated with abuse potential: glutamate, GABA, dopamine, serotonin, histamine, acetylcholine, sigma, opioid, monoamine transporters, potassium channel, calcium channel, chloride channel or sodium channel.

ii. Preclinical Behavioral Studies

a. General Behavioral Responses to Ezogabine in Rats and Monkeys

General Behavior in Rat Toxicity Studies (Study #D23129, D231129, D20443 (2 phases))

In three rat toxicity studies, acute oral administration of ezogabine equivalent to 16 to 32 times the human therapeutic dose produced a reduction in locomotor behavior, ataxia, tremor and decrease in muscle tone. Most animals experienced slight to moderate clonic convulsions. At the highest dose, some animals died within several days of drug administration.

In a fourth rat toxicity study, acute intravenous doses of ezogabine equivalent to 8 to 100 times the human therapeutic dose produced moderate to severe clonic convulsions, decreased muscle tone and loss of righting reflex. At doses equivalent to or greater than 16 times the human therapeutic dose, the majority of animals experienced irregular breathing and cyanosis, followed by death within minutes of drug administration.

General Behavior in Monkey Toxicity Study (Study #3000-922893)

In a single cynomolgus monkey study, acute oral ezogabine produced moderate degrees of ataxia, decreased motor activity, ptosis and salivation at doses equivalent to 2 times the human therapeutic dose, with increasing severity as the dose increased. Tolerance was not observed with continued drug administration over a 10 day dosing period.

b. Self-Administration Studies in Rats (Study # 2007-018)

A self-administration study was conducted in rats to determine if ezogabine has rewarding properties. Animals were initially exposed to the Schedule IV sedative-hypnotic, chlordiazepoxide, so that they would learn to self-administer this drug at levels above those of saline using an FR10 schedule of reinforcement. However, even with dose increases, rats failed to self-administer chlordiazepoxide.

Rats were then exposed to the Schedule II stimulant, cocaine, and were able to learn to self-administer this drug at levels above those produced by saline under an FR10 schedule of reinforcement. When ezogabine was substituted for cocaine, it did not maintain self-administration. Instead, ezogabine produced levels of self-administration that were equivalent to those produced by administration of saline.

iii. Physical Dependence Study in Rats (Study # D23129/FP3395)

A physical dependence study was conducted in rats to determine if discontinuation of ezogabine led to withdrawal signs. The study is inconclusive because no primary data were submitted for evaluation. Rats were treated with oral doses of either ezogabine (equivalent to 3 to 9 times the human therapeutic dose), codeine (an opioid used as a positive control because of its known ability to produce physical dependence) or vehicle for 45 days (6.5 weeks). Once per week during drug administration, ezogabine was discontinued acutely for a day so animals could be rated on an observational battery containing a comprehensive range of withdrawal-associated behaviors, including weight changes, rectal body temperature, diarrhea, Straub tail, changes in respiration, convulsion, exploration, hyperactivity, stereotypy, sniffing and piloerection. Following final drug administration on Day 45, animals were observed using the same battery for 16 days.

Although no primary data were submitted in the study report, the Sponsor states in the narrative that ezogabine did not produce any withdrawal-associated effects during acute drug discontinuation during the dosing period, or after final drug discontinuation. In

contrast, the Sponsor states that codeine produced a transient reduction in weight without any other opioid-associated withdrawal signs or symptoms.

B. Clinical Data Related to Abuse Potential

i. Abuse-Related and Negative AEs in Clinical Efficacy Studies

Overview of Phase 1 Clinical Safety Studies

A total of 21 Phase 1 studies conducted with ezogabine were included in the Integrated Clinical Pharmacology (ICP) Analysis Set (n = 469 healthy subjects). Most of the studies in the ICP evaluated pharmacokinetics, tolerance and safety. (The human abuse potential study was not included in the ICP and is presented separately below). The Sponsor notes that since the majority of the ICP studies were not controlled with placebo, no placebo comparison data are available. The doses of ezogabine tested in the ICP dataset that resulted in adverse events related to abuse potential ranged from 200 to 1650 mg (p.o.).

Overview of Phase 2/3 Clinical Safety Studies

A total of three Phase 2/3 safety and efficacy studies (Study # 3065-A1-205; VRX-RET-E22-301; VRX-RET-E22-302) conducted with ezogabine in patients with seizure disorder were considered as part of the Pivotal Clinical Trial (PCT) dataset (n = 813 patients exposed to ezogabine and 427 exposed to placebo). However, a total of 13 Phase 2/3 safety and efficacy studies were conducted overall with ezogabine in patients with seizure disorder (n = 1365). The Sponsor provided placebo comparisons for only those Phase 2/3 studies that were part of the PCT dataset. The doses of ezogabine tested in the Phase 2/3 studies that resulted in adverse events related to abuse potential ranged from 300 to 1200 mg (p.o.).

Adverse Events in Phase 1 and Phase 2/3 Clinical Trials

Abuse-related adverse events (somnolence, euphoric mood, confusional state, feeling drunk, disorientation, hallucination and feeling abnormal) occurring in Phase 1 studies with healthy individuals and in Phase 2/3 studies with patients who have epileptic conditions are depicted below in Table 1.

The incidence of abuse-related AEs was much higher in Phase 1 ICP clinical studies compared to the incidence in Phase 2/3 clinical studies (see Table 1, below). Specifically, in the Phase 1 studies with healthy individuals who were taking only ezogabine, there was a high rate (5.5-8.5%) of “euphoria”, “feeling drunk” and “confusional state”, accompanied by a notable rate (1.5-1.7%) of “disorientation”, “hallucination” and “feeling abnormal”. Notably, the high rate for “somnolence” (13.4%) in the Phase 1 studies is similar to the rate for this AE produced by placebo (11.9%) in the Phase 2/3 PCT studies.

Table 1:
Incidence of Abuse-Related AEs in Clinical Studies with Ezogabine

Preferred Term AEs	Phase 1 Ezogabine (n = 469)	Phase 2/3 PCT Placebo (n = 427)	Phase 2/3 PCT Ezogabine (n = 813)	All Phase 2/3 Ezogabine (n = 1365)
Somnolence	63 (13.4%)	51 (11.9%)	179 (22.0%)	389 (28.5%)
Euphoric Mood	40 (8.5%)	0	4 (0.5%)	6 (0.4%)
Confusional State	29 (6.2%)	11 (2.6%)	75 (9.2%)	162 (11.9%)
Feeling Drunk	26 (5.5%)	0	7 (0.9%)	20 (1.5%)
Hallucination	23 (4.9%)	0	8 (1.0%)	15 (1.1%)
Disorientation	8 (1.7%)	3 (0.7%)	14 (1.7%)	29 (2.1%)
Feeling Abnormal	7 (1.5%)	0	1 (0.1%)	41 (0.3%)

“PCT” = pivotal clinical trials database

In contrast to the Phase 1 data, the Phase 2/3 data show that individuals with epileptic conditions who were taking ezogabine in combination with other antiepileptic and CNS-active drugs showed a relatively low rate of “euphoria” (0.4-0.5%) but a higher rate of “feeling drunk” (0.9-1.5%) compared to placebo (0% for both AEs) (see Table 1, above). In this clinical population, the rate of “disorientation” (1.7-2.1%, compare to 0.7% from placebo) was similar to that seen in the Phase 1 studies, although the rates of “hallucination (1.0-1.1%, compared to 0% from placebo) and “feeling abnormal” (0.1-0.3%, compared to 0% from placebo) were lower than those seen in the Phase 1 studies. However, there was a much higher rate of “somnolence” in Phase 2/3 studies (22-28.5%, compared to 11.9% from placebo) compared to the rate from Phase 1 studies. However, since somnolence is a known response to many antiepileptic drugs, including the ones that patients were concomitantly taking with ezogabine during the clinical studies, this may be an expected adverse event given the drug interaction profile.

Given the higher rate of abuse-related AEs in Phase 1 studies compared to those in Phase 2/3 studies, a further analysis of these data was conducted in which the total number of incidents of each AE is presented, delineated by dose range (see Table 2, below).

Table 2:
Phase 1 ICP Database Euphoria-Related Adverse Events

Preferred Term AEs (total n = 469)	Total Incidents	100-400 mg	450-750 mg	800-1650 mg
Euphoric Mood (n = 40, 8.5%)	141 incidents	34	72 (58 incidents from 750 mg)	35
Somnolence (n = 63, 13.4%)	105 incidents	38	48 (23 incidents from 750 mg)	19
Hallucination (n = 23, 4.9%)	65 incidents	7	25 (16 incidents from 750 mg)	33
Feeling Drunk (n = 26, 5.5%)	47 incidents	10	18	19
Confusional State (n = 29, 6.2%)	45 incidents	14	15	16
Feeling Abnormal (n = 7, 1.5%)	12 incidents	2	7	3
Disorientation (n = 8, 1.7%)	16 incidents	7	9	0

As seen in Table 2, many subjects who reported an abuse-related AE experienced that AE on multiple occasions. In general, doses above 400 mg produced the greatest number of abuse-related AEs. Of particular note is that the 750 mg dose of ezogabine produced both the highest number of incidents of euphoric mood (n = 58 of 141 total incidents, 41%) and of hallucinations (n = 16 of 65 total incidents, 25%) compared to all other doses. This dose also produced the greatest number of incidents of somnolence (n = 23 of 105 incidents, 22%). The 750 mg dose is less than twice that of the highest single therapeutic dose (400 mg) and is two-thirds of the highest total daily dose (1200 mg). None of the other abuse-related AEs showed a similar pattern of distribution by dose.

Adverse Events in Phase 1 Human Abuse Potential Study

In the Phase 1 human abuse potential study, the incidence of spontaneously-reported AEs related to abuse potential was monitored following administration of placebo, alprazolam (1.5 and 3.0 mg), levetiracetam (4000 mg) and ezogabine (300, 600, 900 mg). As seen in Table 3 (below), somnolence was observed in following administration of all treatments,

but both doses of alprazolam and the highest dose of ezogabine produced the highest levels of this adverse event (57%, 97% and 50%, respectively), compared to placebo (15%). The adverse event of euphoria was reported by subjects following each of the treatments, although the highest response was produced by levetiracetam (40%). The 3.0 mg dose of alprazolam and all three doses of ezogabine (300, 600 and 900 mg) also produced high levels of euphoria (17%, 18%, 21% and 33%, respectively), compared to placebo (8%). Given that the 900 mg dose of ezogabine was terminated from the protocol following serious adverse cardiac effects following administration to only 6 subjects, it is not possible to determine the true incidence of euphoria resulting from administration of this dose. These euphoria data are consistent with the Phase 1 ICP AE profile with ezogabine. In contrast, hallucination was reported as an AE in the human abuse potential study following administration of the 1.5 mg dose of alprazolam (4%) and ezogabine (17%).

Table 3:
Incidence of Abuse-Related AEs in Human Abuse Potential Study with Ezogabine

AE	Placebo	Alpraz 1.5 mg	Alpraz 3.0 mg	Levet 4000 mg	Ezog 300 mg	Ezog 600 mg	Ezog 900 mg
Somnolence	4 (15%)	16 (57%)	29 (97%)	10 (33%)	6 (18%)	5 (15%)	4 (67%)
Euphoric mood	2 (8%)	1 (4%)	5 (17%)	12 (40%)	6 (18%)	7 (21%)	2 (33%)
Hallucination	0	1 (4%)	0		0	0	1 (17%)

“Alpraz” = alprazolam, “Levet” = levetiracetam, “Ezog” = ezogabine

ii. Phase 1 Human Abuse Potential Study (Study # VRX-RET-E22-108)

Study Design

A human abuse potential study with a randomized, double-blind, placebo- and active comparator-controlled single dose crossover design was conducted in individuals with a history of CNS-depressant abuse (n = 26 study completers). The study had three phases: 1) Qualifying Phase (administration of alprazolam (2.0 mg) and placebo), 2) Treatment Phase (administration of ezogabine (300, 600 and 900 mg), alprazolam (1.5 and 3.0 mg; positive control), levetiracetam (4000 mg; “negative control”) and placebo) and 3) Follow-Up Phase

The proposed therapeutic daily dose of ezogabine ranges from 200-400 mg TID. Thus, the 300 mg dose represents a median single dose within the therapeutic range. The two higher doses in the human abuse potential study (600 and 900 mg) are 2 and 3 times

greater than the therapeutic dose. Use of the 900 mg dose of ezogabine was terminated, however, after it produced serious cardiac-related adverse events in two of six subjects, including a case of nonfatal, spontaneously resolving asystole reported as a cardiac arrest and a case of nonfatal ventricular tachycardia.

Alprazolam was selected as a positive control because it has anticonvulsant properties and has known abuse potential as a Schedule IV sedative-hypnotic under the CSA. The 1.5 and 3.0 mg doses of alprazolam were chosen based on their use in previous human abuse potential studies as doses that differentiate from placebo on positive subjective measures.

Levetiracetam (4000 mg) was selected by the Sponsor as a “negative control”, because it is an antiepileptic drug that is not scheduled under the CSA, with a similar adverse event profile to that of ezogabine, including published reports of abuse-related subjective responses (Feltner and Haig, 2010; Wade et al., 2010). However, justification of levetiracetam as a “negative control” was not provided. Old, unscheduled drugs, such as levetiracetam, may not have undergone a thorough abuse potential evaluation prior to marketing. This means that an unscheduled drug may produce positive subjective responses in clinical trials, but without a formal analysis, it is not clear how to interpret the results.

Subjective and Cognitive Measures Outcome Data and Discussion

The Sponsor identified four primary positive subjective measures: VAS-Drug Liking (bipolar scale, 0-100), VAS-Overall Drug Liking (bipolar scale, 0-100), ARCI-MBG (Euphoria; unipolar scale, 0-16) and VAS-Take Drug Again (unipolar scale, 0-100).

Table 4 (below) depicts peak responses (Emax over the first 8 hours after drug administration) for these measures following administration of placebo, alprazolam (A; 1.5 and 3.0 mg), and ezogabine (E; 300 and 600). These data show that alprazolam produced statistically significant increases on all four of the primary measures compared to placebo, which validates the study. Ezogabine also produced statistically significant increases on the four measures compared to placebo (with the exception of Drug Liking for the 600 mg dose), and these increases were statistically similar to those produced by both doses of alprazolam.

Three secondary positive subjective measures (VAS-High, VAS-Good Effects and ARCI-Amphetamine (Activation)) were also evaluated following administration of placebo, alprazolam (1.5 and 3.0 mg), and ezogabine (300 and 600) (data not shown). On all three of these measures, alprazolam and ezogabine produced statistically significant increases compared to placebo. There were no statistical differences between the increases in response on these measures resulting from ezogabine and alprazolam administration at either of the doses tested for each drug.

Table 4:
Primary Positive Endpoints: Mean Emax (+ S.E.) for VAS and ARCI Scores

Scale (value range)	Placebo	Alprazolam 1.5 mg	Alprazolam 3.0 mg	Ezogabine 300 mg	Ezogabine 600 mg
VAS – Drug Liking (0-100; <i>bipolar scale,</i> <i>neutral = 50</i>)	54.7 ± 3.7	74.7 ± 3.5 *	78.8 ± 3.2 *	70.8 ± 3.6 *	77.0 ± 3.4
VAS – Overall Drug Liking (0-100; <i>bipolar scale,</i> <i>neutral = 50</i>)	52.7 ± 4.6	67.2 ± 4.4 *	71.6 ± 4.2 *	62.6 ± 4.5 *	70.2 ± 4.3 *
ARCI – MBG (Euphoria) (0-16; <i>unipolar scale,</i> <i>neutral = 0</i>)	1.0 ± 0.9	5.8 ± 0.9 *	6.6 ± 0.8 *	4.6 ± 0.9 *	5.7 ± 0.9 *
VAS – Take Drug Again (0-100; <i>unipolar scale,</i> <i>neutral = 0</i>)	35.9 ± 7.1	66.2 ± 6.8 *	68.0 ± 6.5 *	57.1 ± 7.0 *	69.1 ± 6.6 *

VAS = visual analog scale, ARCI = Addiction Research Center Inventory
Values shown are mean of Emax (± s.e.), * = p < 0.05 compared to placebo

(Source: DARRTS, NDA 22-345, Biometrics Review, Dr. Ling Chen, April 23, 2010)

Three secondary negative subjective (VAS-Bad Effects (unipolar scale, 0-100), ARCI-LSD (Dysphoria; unipolar scale, 0-13), ARCI-PCAG (Sedation; unipolar scale, 0-15)) were evaluated following administration of placebo, alprazolam (1.5 and 3.0 mg), and ezogabine (300 and 600). Table 5 (below) depicts peak responses (Emax over the first 8 hours after drug administration) for these measures. These data show that both alprazolam and ezogabine produced statistically significant increases on these three negative measures compared to placebo. However, ezogabine produced negative subjective responses that were statistically significantly less than or similar to those produced by alprazolam.

Table 5:
Secondary Negative Endpoints: Mean Emax (+ S.E.) VAS and ARCI Scores

Scale (value range)	Placebo	Alprazolam 1.5 mg	Alprazolam 3.0 mg	Ezogabine 300 mg	Ezogabine 600 mg
VAS – Bad Effects (0-100; <i>unipolar scale,</i> <i>neutral = 0</i>)	25.1 ± 28.0	45.3 ± 31.0 *	66.7 ± 25.4 *	36.5 ± 27.6 * `	53.3 ± 26.2 *
ARCI – LSD (Dysphoria) (0-13; <i>unipolar scale,</i> <i>neutral = 0</i>)	1.2 ± 1.7	3.5 ± 2.0 *	4.0 ± 1.6 *	2.5 ± 2.5 *	4.1 ± 2.7
ARCI – PCAG (Sedation) (0-15; <i>unipolar scale,</i> <i>neutral = 0</i>)	1.1 ± 1.3	8.0 ± 2.8 *	8.9 ± 2.6 *	5.2 ± 3.3 * ^ `	5.6 ± 3.4 * ^ `

VAS = visual analog scale, ARCI = Addiction Research Center Inventory
Values shown are mean of Emax (± s.e.), * = p < 0.05 compared to placebo;
^ = p < 0.05 compared to alprazolam 1.5; ` = p < 0.05 compared to alprazolam 3.0

(Source: DARRTS, NDA 22-345, Biometrics Review, Dr. Ling Chen, April 23, 2010)

Based on limited data (n = 6) for which a statistical analysis could not be conducted, the 900 mg dose of ezogabine produced Emax values on two positive subjective measures (Drug Liking and Good Effects) that were numerically higher than those reported for the lower doses of ezogabine and either dose of alprazolam. Additionally, the 900 mg dose of ezogabine produced Emax values on two negative subjective effects (Bad Effects and Dysphoria) that were numerically less than or similar to those observed for the lower doses of ezogabine and either dose of alprazolam. In the study report, the Sponsor states, that the 900 mg dose of ezogabine produced “multiple AEs such as somnolence, euphoric mood, amnesia, visual disturbance, hypoaesthesia, paranoia, fear, confusion, and hallucination.” Thus, in the context of the serious cardiac adverse events associated with the 900 mg dose, ezogabine produces a serious safety risk at a dose three times that of a single therapeutic dose.

Finally, ezogabine did not produce a statistically significant impairment in performance on two cognitive measures, Choice Reaction Time (a measure of whether a drug slows response time) and Divided Attention (a measure of whether a drug interferes with the ability to monitor two tasks at once). In contrast, alprazolam produced statistically

significant impairment on both measures. This demonstrates again that ezogabine produces fewer negative cognitive responses than alprazolam.

iii. Phase 1 Ezogabine Interaction Study with Ethanol (Study # VRX-RET-E22-107)

Study Design

A randomized, double-blind, crossover Phase 1 clinical drug interaction study was conducted in healthy volunteers with a history of moderate alcohol consumption (up to 28 drinks/week). Subjects first participated in a qualification phase to ensure they could distinguish ethanol (1 g/kg body weight, 40% ethanol in the form of vodka, p.o.) from placebo ethanol (apple juice). Subjects who qualified then received four oral treatments: ethanol placebo (apple juice) plus ezogabine placebo, 200 mg ezogabine plus ethanol placebo (apple juice), ethanol (1 g/kg body weight) plus ezogabine placebo; ethanol (1 g/kg body weight) plus 200 mg ezogabine. The 200 mg dose of ezogabine represents the lowest single therapeutic dose.

Subjective Measure Outcome Data

Five visual analog scale (VAS) subjective measures were used to evaluate whether drug treatments altered subjective experiences. The two ethanol conditions (ethanol alone or ethanol plus ezogabine), but not ezogabine alone, produced increased ratings on VAS-Intoxication and VAS-Feel Sick compared to placebo, with the combination producing a slightly higher increase compared to ethanol alone. All three drug treatments increased rating on VAS-Dizziness compared to placebo and decreased ratings on VAS-Attention Span Good and VAS-Vision Crisp compared to placebo.

Balance Platform (Eyes Closed)

A balance platform was used to determine whether the drug treatments altered subjects' ability to stand and remain stable with their eyes closed. Ezogabine alone did not appreciably alter balance compared to placebo. In contrast, both conditions involving ethanol (ethanol alone and ethanol plus ezogabine) produced an increase in impairment in balance compared to placebo (ellipse area, center of pressure velocity and center of pressure path length), without appreciable differences between the two conditions.

Cognitive Measures

The Choice Reaction Time test and the Divided Attention test were used to evaluate whether the drug treatments altered cognitive performance. On the Choice Reaction Time test, both ethanol conditions (ethanol alone and ethanol plus ezogabine) produced an increase in total reaction time, motor reaction time and recognition reaction time compared to placebo. On the Divided Attention test, both ethanol conditions (ethanol alone and ethanol plus ezogabine) increased mean hit latency but decreased percent over

the road scores and percent target hits compared to placebo. Ezogabine alone did not appreciably alter performance on either test compared to placebo.

Pharmacokinetics

Pharmacokinetic data show that ethanol slightly increases the C_{max} of ezogabine levels compared to ezogabine alone (636 ng/ml vs. 530 ng/ml, respectively) and concomitantly increases the AUC (0-8 hr) values (2433 hr*ng/ml vs. 1894 hr*ng/ml). In contrast, ezogabine does not alter the pharmacokinetics of ethanol with C_{max} values remaining ~34 mmol/l and AUC (0-8 hr) values remaining ~ 161 hr*mmol/l after each drug treatment.

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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/

KATHERINE R BONSON
06/30/2010

SILVIA N CALDERON
06/30/2010

MICHAEL KLEIN
06/30/2010

Date: June 3, 2010

From: OCP Safety Review Team

To: OCP Pediatric Group

Subject: Safety Consult to NDA 22345 (retigabine)

This memo responds to your consult to us dated May 20, 2010 regarding the key safety assessments to be included the Proposed Pediatric Study Request for NDA 22345

Background: Retigabine, a human KCNQ2 and KCNQ3 K⁺ channels opener, is currently under review for approval. The proposed indication is adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization.

The proposed dosing regimen:

Administer in 3 divided doses daily with or without food.

- Begin dosing at 300 mg/day for 1 week.
- Titrate to maintenance dose by increasing the dose in weekly intervals of up to 150 mg/day.
- Optimize effective dose between 600 to 1,200 mg/day.

What serious treatment-related adverse events are reported in the submitted NDA?

Dose-dependent serious adverse events reported by the sponsor over the dose range of 600 mg/day to 1,200 mg/day included dizziness, somnolence, confusional state, tremor, coordination abnormal, memory impairment, headache, vision blurred, speech disorder, urinary tract infection, gait disturbance, convulsion, aphasia, balance disorder, constipation, and nausea. The majority of these side effects are treatment related and experienced by >5% of the safety population (all phase 2 and 3 trials combined). Of concerns, urinary/renal disorders included chromaturia, hematuria, and renal impairment/insufficiency, and contributed to discontinuation. Increases in hepatic enzymes were reported in 3% of 813 safety population. Treatment-related serious adverse events included encephalopathy, confusional state, suicidal ideation, and nausea in the retigabine 1200 mg/day group.

What pharmacological actions of retigabine are known?

Retigabine interacts with neuronal Kv7 subunits (Kv7.2–Kv7.5) by acting as Kv7 channel openers and also enhances GABA_A currents(1) Retigabine shifts the activation curve of I_M toward hyper-polarization and reduces firing frequency in various brain regions, including hippocampal and sympathetic neurons. I_M, a

non-inactivating, slowly deactivating sub-threshold K^+ current, opposes depolarizing current and stabilizes membrane potential.

The M current (I_M) through the heteromeric assembly of K^+ channel subunits encoded by KCNQ2 and KCNQ3 subunits are muscarinic-regulated.(2) Retigabine inhibits the K^+ -evoked release of norepinephrine, D-aspartate, and GABA release via KCNQ2 in hippocampal nerve terminals.(3)

What plausible treatment-induced adverse reactions can be hypothesized based on the pharmacological actions of retigabine?

Impact on cognition

Retigabine inhibited the release of norepinephrine, aspartate, and GABA from hippocampal nerve terminals. (2) Inhibitors of Kv7 channels, linopirdine and XE-991, were once developed for cognition enhancement. (4) These Kv7 channel blockers inhibited activation of these channels by retigabine.(2) Therefore, it is plausible that chronic use of retigabine may cause cognitive impairment.

Impact on memory and learning

Retigabine suppressed gamma and kainate-induced theta-like oscillations in the rat hippocampus.(5) Hippocampal oscillation network was hypothesized to play a role in memory(6, 7). Kv7 channel openers was suggested to impair learning and memory.(8) D-aspartate was suggested to be involved in memory(9) and its release is inhibited by retigabine(3). Based on these reports, chronic use of retigabine may impair learning.

Impact on smooth muscles (intestine, bladder and vascular)

Voltage-gated K^+ channels (Kv7) are also widely expressed in smooth muscles. Retigabine was shown to reduce the contractility and tone of bladder tissue.(10) In freely moving rats, retigabine increased voided volume but decreased maximal bladder pressure and voiding intervals.(11) Furthermore, retigabine relaxed vascular smooth muscle including aortic and venous muscles through acting on the Kv channels.(12) This effect of retigabine apparently agrees with the adverse events of urinary retention and constipation reported in the submitted NDA.

Impact on dopamine release

K^+ -evoked dopamine release from rat striatal synaptosomes was blocked by retigabine and the blockage was reversed by Kv7 blockers.(2, 13) Drug-induced Parkinsonism is known to occur with use of antiepileptics, antidepressants, and drugs for treating vertigo, and can persist even after the causative drug is discontinued.(14) The possibility of retigabine inducing Parkinsonism-related symptoms seems to be consistent with the adverse events of gait disturbance and balance disorders reported in the submitted NDA.

Are there other treatment-related adverse events that warrant monitoring?

Antiepileptic drugs have been linked to suicidality based on the studies which showed that patients taking antiepileptic drugs were at a higher risk of suicide as compared to those taking placebo.(15) The sponsor reported suicide attempts and suicide ideation, but no death.

Increases in liver enzymes were observed in 3% of the safety population of 813 subjects. The possibility of hepatotoxicity should not be ruled out.

Conclusion and safety comments for the Pediatric Group of OCP:

Many serious adverse events reported are in general in agreement with the pharmacological actions of retigabine.

1. Children with impaired renal function or familiar history of renal impairment should avoid retigabine.
2. Clinical development of urinary retention and related renal impairment should be closely monitored.
3. Since retigabine is proposed as adjunctive treatment for epilepsy, co-administration of those antiepileptic drugs that can cause Parkinsonism should be avoided. Clinical manifestations of Parkinson's symptoms should be monitored regularly, especially for those who have familiar history of, or carry the genes identified to be at risk of developing, Parkinson's disease.
4. Clinical signs of impaired learning and cognition should be monitored. For those children who are already learning-challenged, use of this drug should be avoided.
5. Children on medications that are known to cause depression and suicidal ideation or with a familiar history of suicide should avoid retigabine. Precaution should be taken to monitor the patients' propensity for suicidal ideation.
6. Liver injury should be monitored especially in those who are also on other medications that are known to cause liver injury.

Appendices

Key safety data from the submitted NDA

Table 46 TEAEs Leading to Discontinuation Reported by More Than 2% of Patients in Any Treatment Group (Safety Population: PCT)

Preferred Term	Number (%) of Patients				
	Placebo (N=427)	RTG 600mg/day (N=281)	RTG 900g/day (N=273)	RTG 1200mg/day (N=259)	RTG Total (N=813)
Any event leading to d/c	45 (10.5)	49 (17.4)	69 (25.3)	81 (31.3)	199 (24.5)
Dizziness	5 (1.2)	9 (3.2)	16 (5.9)	21 (8.1)	46 (5.7)
Confusional state	4 (<1.0)	4 (1.4)	8 (2.9)	20 (7.7)	32 (3.9)
Somnolence	4 (<1.0)	7 (2.5)	13 (4.8)	8 (3.1)	28 (3.4)
Fatigue	1 (<1.0)	9 (3.2)	12 (4.4)	6 (2.3)	27 (3.3)
Vertigo	4 (<1.0)	5 (1.8)	5 (1.8)	6 (2.3)	16 (2.0)
Coordination abnormal	3 (<1.0)	2 (<1.0)	5 (1.8)	9 (3.5)	16 (2.0)
Disturbance in attention	0	3 (1.1)	5 (1.8)	6 (2.3)	14 (1.7)
Headache	2 (<1.0)	3 (1.1)	5 (1.8)	6 (2.3)	14 (1.7)
Tremor	0	1 (<1.0)	4 (1.5)	7 (2.7)	12 (1.5)
Dysarthria	0	3 (1.1)	1 (<1.0)	6 (2.3)	10 (1.2)
Convulsion	7 (1.6)	2 (<1.0)	1 (<1.0)	6 (2.3)	9 (1.1)

Table 108 Hepatic Enzyme Adverse Events (Safety Population: PCT)

Preferred Term	Number (%) of Patients				
	Placebo N=427	Retigabine			
		600mg/day N=281	900mg/day N=273	1200mg/day N=259	Total N=813
Any hepatic enzyme event ¹	6 (1.4)	6 (2.1)	9 (3.3)	9 (3.5)	24 (3.0)
GGT increased	2 (0.5)	0	5 (1.8)	3 (1.2)	8 (1.0)
ALT increased	1 (0.2)	1 (0.4)	1 (0.4)	3 (1.2)	5 (0.6)
Liver function test abnormal	0	2 (0.7)	2 (0.7)	1 (0.4)	5 (0.6)
AST increased	2 (0.5)	0	1 (0.4)	1 (0.4)	2 (0.2)
Hepatic enzyme increased	0	2 (0.7)	0	0	2 (0.2)
Transaminases increased	0	0	1 (0.4)	1 (0.4)	2 (0.2)
Hepatic function abnormal	1 (0.2)	1 (0.4)	0	0	1 (0.1)
Blood alk phos abnormal	0	0	0	1 (0.4)	1 (0.1)
Blood alk phos increased	2 (0.5)	0	0	0	0

1. Preferred terms were combined to give an overall incidence for hepatic enzyme events – see Appendix 7.4 for grouping of terms

Adverse events are presented in descending order of the proportion of patients for whom the event was reported in the Total RTG group.

Alk phos = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT= gamma-glutamyl transferase

Data Source: [Table 20.02](#) and [Table 7.05](#)

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JANE PF BAI
06/03/2010

DARRELL ABERNETHY
06/03/2010

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/

PEIFAN J BAI

06/22/2010

This review is in response to pediatric group's request for providing inputs regarding safety monitoring in pediatric studies.

DARRELL R ABERNETHY

06/22/2010

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: April 12, 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Ta-Chen Wu, Ph.D., Clinical Pharmacology Reviewer, OCP
Angela Yuxin Men, M.D., Ph.D., Clinical Pharmacology Team Leader, OCP
Office of Clinical Pharmacology

FROM: Stephanie N. Keefe, Regulatory Health Project Manager/DNP

SUBJECT: Request for Biopharmaceutical Inspections
NDA 22-345
Potiga (retigabine) tablets, 50mg, (b) (4) 200mg, 300mg, 400mg
Valeant Pharmaceuticals North America

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
RTG113287	Study Centre: Charles River Clinical Services Northwest, Inc. 3615 Pacific Avenue, Tacoma, WA 98418, The United States of America Investigator: Bianchi, Elizabeth, MD. Investigator/Centre Number: 143852 / 068164 Initiation Date: 16 JUL 2009 Completion Date: 10 SEP 2009 Date of Report: FEB 2010	(b) (4)

		(b) (4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

_____ There is a lack of domestic data that solely supports approval;

Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **earliest possible date**. We intend to issue an action letter on this application by **August 30, 2010**.

Should you require any additional information, please contact *Stephanie N. Keefe, RPM*, at 301-796-4098 or *Ta-Chen Wu, Ph.D.*, at 301-796-1632.

.

Concurrence: (Optional)

Ta-Chen Wu, Ph.D., Clinical Pharmacology Reviewer, OCP

Angela Yuxin Men, M.D., Ph.D., Clinical Pharmacology Team Leader, OCP

Appendix.

EDR Location: <\\CDSESUB1\EVSPROD\NDA022345\022345.enx>

EDR Location: <\\CDSESUB1\EVSPROD\NDA022345\0018>

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Cover Letter: <\\CDSESUB1\EVSPROD\NDA022345\0018\m1\us\102-cover-letters\cover.pdf>

Application Type/Number: nda022345

Incoming Document Category/Sub Category: Electronic_Gateway

Incoming Document Category/Sub Category Number: 0019

Letter Date: 04/09/2010

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/

STEPHANIE N KEEFE
08/19/2010

Memorandum of Consultation

From:

Chong M. Kim, MD/PhD (Medical Officer – DRUP)
Mark S. Hirsch, MD (Clinical Team Leader – DRUP)
George Benson, MD (Deputy Director – DRUP)

To: Stephanie N. Keefe (DNP)

Re: NDA 22-345 Potiga (Retigabine) Tablets

Date of consultation request: Dec 15, 2009

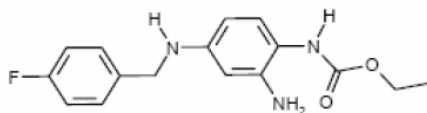
Date consultation completed: Feb 24, 2010

Background:

Partial-onset seizures are the most common type of seizures in adult patients. It is estimated that up to 30% of patients with epilepsy have either intractable or uncontrolled seizures or have significant adverse side effects secondary to medication limiting their ability to appropriately control their epilepsy with medication. NDA 22-345 was received on October 30, 2009, and provides for adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization. The international clinical program described in this NDA is comprised of 44 studies, including 28 Phase I studies, 5 completed Phase II studies, 2 completed Phase III studies and 6 long-term, open-label extension studies.

Retigabine, N-[2-amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, is a first in class neuronal potassium (KCNQ) channel opener-potentiator for the treatment of partial-onset seizures.

The molecular and structural formula is shown below:



Retigabine: Molecular Formula, C₁₆H₁₈FN₃O₂

The KCNQ genes encode a family of voltage-dependent ion channels that maintain cellular membrane potential, regulate neurotransmitter release, and control subthreshold electrical excitability in neurons. It's recommended by the Sponsor that the initial dose should be 100 mg three times daily (300 mg/day) and increased at weekly intervals by a maximum of 150 mg/day, given as three divided doses, up to a recommended maximum dose of 600 to 1,200 mg/day based on individual patient response and tolerability.

Reason for DRUP Consult:

1. Several cases of urinary retention / bladder atony were 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

Questions posed by DNP:

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 detrusor 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, i.e., 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?

Material reviewed:

Relevant material in NDA 22-345 package

The submission may be accessed at :

<\\CDSESUB1\\EVSPROD\\NDA022345\\022345.ENX>.

Consultant's response to questions posed by DNP:

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 detrusor muscle to produce weakness of contraction?

DRUP response: Available preclinical and clinical data indicate that retigabine acts directly on the detrusor muscle to interfere with bladder 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?

DRUP response: The cases of clinical AEs encompassing urinary retention demonstrated recovery of bladder function after discontinuation of retigabine. Retigabine does not appear to cause direct permanent alteration of detrusor function, however, repeat episodes of severe urinary retention or chronic bladder distension which are not clinically apparent may cause permanent bladder injury through ischemia, infection, urolithiasis, inflammation, and loss of normal bladder cycling function.

3. If needed in labeling, what is the best approach to monitoring for this adverse effect, i.e., symptom profile from the AUA scale, periodic bladder ultrasound, patient symptoms alone or some combination of the aforementioned parameters?

DRUP response: Periodic clinical query of any voiding dysfunction and bladder ultrasound for post –void residual are both recommended to monitor for this AE.

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?

DRUP response: Yes. Human pharmacology and metabolism data indicate that up to 40% of retigabine dosed can be excreted intact in the urine. CMC data indicate that retigabine is not soluble in aqueous solution at normal physiologic urine pH. The sponsor states that the unknown urinary crystals are found only in retigabine treated patients. Mass spectrometry evaluation of the unknown crystals identified peaks corresponding to the known molecular weight of retigabine and retigabine dimers.

Retigabine crystalluria presents a theoretical risk of acute renal (upper tract) injury due to intratubular precipitation and urolithiasis, however, this is not clinically apparent in the Phase 3 safety data. Crystalluria alone does not pose a threat to bladder (lower tract) function in patients with normal GU tract anatomy and function.

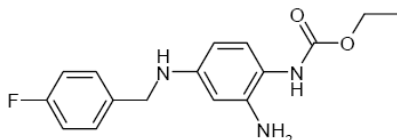
5. Is there an approach to monitoring pre-emptively for crystal formation?

DRUP response: Yes. Baseline and periodic microscopic urinalysis could be obtained in all patients who receive retigabine to assess for subclinical crystalluria. It might be feasible to use crystalluria as a marker for possible dose reduction or for additional testing for the presence of urinary stones. Clinically significant urolithiasis can be monitored with baseline and periodic imaging with bladder sonogram, renal sonogram, and KUB radiography.

Consultant's summary and outlier analysis:

Relevant CMC information:

Figure 1 Chemical Structure of Retigabine



The retigabine molecular formula is C₁₆H₁₈FN₃O₂ and the molecular mass is 303.3 daltons.

Retigabine shows

(b) (4)

All significant nonclinical, clinical, and formulation studies with retigabine were performed using

(b) (4)

Table 1. Retigabine Unit Cell Crystal Data

Attribute	Results
(b) (4)	

Retigabine is not soluble in aqueous solution of 0.1 N NaCl or in aqueous solution with normal physiological range of urine pH.

Table 2. Solubility profile of Retigabine in Various Solvents at (b) (4)

Solvents	Solubility (g/L)	USP/Ph. Eur. Solubilities
Water	(b) (4)	Practically insoluble
(b) (4)		

Table 3. pH Solubility Profile of Retigabine in Aqueous Media at (b) (4)

Solution pH at 37°C	Solubility of Retigabine in g/L
(b) (4)	

Relevant preclinical studies:

In addition to their expression in neurons, KCNQ channels are also found in vascular smooth muscle, urinary bladder, and intestine. RT-PCR revealed that KCNQ1, KCNQ3 and KCNQ5 are expressed in the rat urinary bladder smooth muscle cells, with KCNQ5 being the most highly expressed. Retigabine (RTG) hyperpolarized the resting membrane potential in the isolated rat bladder smooth muscle cells and increased outward K⁺ current. When cells were held at -50 mV, RTG (10 µM) significantly and reversibly increased outward current at test potentials above -20 mV.

Consistent with these *in vitro* observations, in the hypertrophied bladder model RTG decreased the frequency of spontaneous bladder contractions, while in the neurogenic bladder model RTG blocked micturition in a dose-dependent manner. Various urinary bladder effects including distension and associated effects in kidneys have been observed in mouse, rat, and dog toxicity studies. In a 14-day oral gavage mouse repeat-dose toxicity studies, macroscopic observations included distended abdomen, focal lesions of the penis, hematuria, and yellow discoloration of the abdominal wall (fur removed). Fluid in the abdominal cavity, seen in early decedent animals with higher doses of RTG, was presumed to be a result of bladder perforation. In addition, a thickened bladder wall and bladder calculi were seen in RTG-treated mice. Further observations at necropsy included dilatation of ureters, discolored renal cortices, and renal pelvic dilatation (hydronephrosis). The urinary system toxicities elicited by RTG were sufficiently marked as to be considered unlikely to allow a sufficient rate of long-term survival of study animals.

Relevant human pharmacology and metabolism:

Retigabine is generally rapidly absorbed after single or multiple dosing and the absolute bioavailability of retigabine immediate release formulations is approximately 60%. Time to maximum concentration (t_{max}) values typically range from 0.5 to 2.0 hours with a half-life ($T_{1/2}$) of 6 to 10 hours. Population pharmacokinetic analysis determined that retigabine clearance increases with the increasing body surface area and that no dosage adjustments are necessary due to gender. Metabolism is extensively through formation of the N-acetyl metabolite of retigabine (NAMR) and through N-glucuronidation of both retigabine and NAMR. There is no evidence for oxidative metabolism via P450 enzymes. Retigabine is mainly eliminated through the renal route, as evidenced by 84% of total radioactivity recovered in the urine, with unchanged parent compound in urine accounting for 36% of the administered dose.

Focused review of relevant human clinical studies:

The evidentiary requirements for efficacy and safety are supported principally by results from three adequate and well-controlled studies in patients with partial-onset epilepsy: a Phase IIb study (conducted by Wyeth), Study 3065A1-205 (Study 205) and two Phase III studies conducted by Valeant, Study VRX-RET-E22-301 (Study 301) and Study VRXRET-E22-302 (Study 302). Data collected through December 31, 2008, is provided in this NDA. The Integrated Summary of Safety (ISS) has a safety database cut off for completed/ongoing studies that includes collection of all records from scheduled visits and resolution of database queries through June 30, 2008.

Table 4. Outline of Pivotal Efficacy Studies 205, 301, and 302

	Study 205	Study 301	Study 302
Phase/Sponsor	IIb/Wyeth	III/Valeant	III/Valeant
Treatment Group	600, 900, 1200 mg/day, PBO	1200 mg/day, PBO	600, 900 mg/day, PBO
Dosage Forms Used	50 mg, 100 mg or 200 mg IR capsules (note: 600 mg dose = 2X100 mg capsule TID; 900 mg dose = 3X100 mg capsule TID; 1200 mg dose = 1X 200 mg and 2X 100 mg capsule TID)	50 mg, 100 mg, 300 mg IR tablets (note: 1200 mg dose = 1X 300 mg tablet and 2X 50 mg tablets TID)	50 mg and 100 mg IR tablets (note: 300 mg dose = 3X 100 mg tablets TID)
Duration of Double-blind	16 weeks	18 weeks	16 weeks
Duration of Titration	8 weeks	6 weeks	4 weeks
Duration of Maintenance	8 weeks	12 weeks	12 weeks
Countries	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland Portugal, Slovakia, Spain, Sweden, UK, and US	Argentina, Brazil, Canada, Mexico, and US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, S Africa, Spain, UK Ukraine, and US

Study 205

- A randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging study to evaluate the efficacy and safety of retigabine administered as add-on therapy in patients with partial epilepsy.
- The primary objective was to evaluate the efficacy and safety of 3 times daily (TID) administration of 3 different doses (200, 300, and 400 mg) of retigabine compared with placebo, all of which were administered as add-on therapy in patients with partial epilepsy who were receiving 1 or 2 of the following established treatments: valproic acid, carbamazepine, phenytoin, topiramate, lamotrigine, gabapentin, oxcarbazepine, benzodiazepines, or barbiturates and vagal nerve stimulation.
- The study consisted of an 8-week screening and baseline phase, during which patients were evaluated for seizure frequency; an 8-week titration phase; an 8-week maintenance phase,* during which patients received the dose reached at the end of the titration phase; and a 5-week interim phase, during which the retigabine dose was adjusted to 300 mg TID for all patients.
- 399 men and women aged 16 to 70 years were randomized; 397 were analyzed for safety; and 396 were analyzed for efficacy (ITT population)

Table 5. Mean overall duration of therapy – safety population

Parameter	Placebo (N = 96)	200 mg TID (N = 100)	300 mg TID (N = 95)	400 mg TID (N = 106)	Total (N = 397)
Duration (days) of therapy^a					
Mean ± SD	131.1 ± 46.26	127.8 ± 47.02	122.8 ± 49.94	108.7 ± 56.14	122.3 ± 50.68
Median	147	147	147	147	147
Minimum, Maximum	1, 175	4, 169	4, 172	1, 177	1, 177

- Table 6. Urogenital sytem treatment emergent adverse events reported during the double blind phase (titration and maintenance periods)

Coded term	Number (%) of patients			
	Placebo (N= 96)	Retigabine		
		200 mg TID (N = 100)	300 mg TID (N = 95)	400 mg TID (N = 106)
Urine abnormality	0	4 (4.0)	3 (3.2)	4 (3.8)
Hematuria	1 (1.0)	1 (1.0)	2 (2.1)	2 (1.9)
Urinary tract infection	3 (3.1)	2 (2.0)	3 (3.2)	2 (1.9)
Urinary frequency	0	0	1 (1.1)	2 (1.9)
Dysuria	0	0	0	2 (1.9)
Urination impaired	0	0	3 (3.2)	1 (0.9)
Kidney pain	1 (1.0)	0	2 (2.1)	1 (0.9)
Impotence	0	1 (1.0)	1 (1.1)	1 (0.9)
Cystitis	0	0	0	1 (0.9)
Prostatic disorder	0	0	0	1 (0.9)
Fibrocystic breast	0	0	0	1 (0.9)
Menopause	0	0	0	1 (0.9)
Albuminuria	0	1 (1.0)	0	0
Epididymitis	1 (1.0)	1 (1.0)	0	0
Kidney failure	0	1 (1.0)	0	0
Ovarian disorder	0	1 (1.0)	0	0
Oliguria	0	1 (1.0)	0	0
Urinary urgency	0	1 (1.0)	0	0
Dysmenorrhea	2 (2.1)	0	0	0
Amenorrhea	1 (1.0)	0	0	0
Ovarian cyst	1 (1.0)	0	0	0
Vaginitis	1 (1.0)	0	0	0
Presented in order of decreasing frequency in the retigabine 400 mg TID group. Note that the scheduled dose might not have been reached at the time of the occurrence of the event. Source: Table V 5.3 (Section 14.3.1)				

- One patient in this study experienced kidney failure due to obstructive uropathy (Patient 0448 in the 200mg TID group). This 53 y/o female started therapy on 4/5/2000 and AE started on 4/24/2000. During participation in the Retigabine protocol, the patient was noted to have a post catheterization urinary volume of 1500cc, serum creatinine of 4.5 mg/dL and hydronephrosis. Renal and voiding function normalized after a period of post-obstructive diuresis.
- The proportion of patients with urine amorphous sediment of potential clinical importance tended to increase with retigabine dose during the titration and maintenance phases. At the end of maintenance period, the proportion of patients with potentially important values for this parameter were 52% placebo, 73% 200 mg TID, 69% 300 mg TID, and 84% 400 mg TID.

- Table 7. The proportion of patients with urine amorphous sediment.

Parameter	n/N (%) ^a of subjects			
	Placebo	Retigabine 200 mg TID	Retigabine 300 mg TID	Retigabine 400 mg TID
Urine acetone/ketones				
Baseline	10/91 (11)	4/90 (4)	8/91 (9)	9/96 (9)
Titration	18/91 (20)	21/94 (22)	19/90 (21)	14/98 (14)
Maintenance	9/77 (12)	21/80 (26)	16/74 (22)	10/65 (15)
Urine amorphous sediment				
Titration	16/28 (57)	44/64 (69)	47/68 (69)	64/72 (89)
Maintenance	11/21 (52)	41/56 (73)	38/55 (69)	43/51 (84)
Urine bacteria				
Titration	16/58 (28)	26/78 (33)	22/74 (30)	29/80 (36)
Maintenance	13/45 (29)	19/60 (32)	19/59 (32)	20/54 (37)
Urine calcium oxalate, crystals ^b				
Titration	13/18 (72)	12/17 (71)	6/10 (60)	12/17 (71)
Maintenance	7/12 (58)	6/11 (55)	6/9 (67)	2/5 (40)
Urine hemoglobin blood				
Baseline	13/91 (14)	10/90 (11)	9/91 (10)	14/96 (15)
Titration	21/91 (23)	20/94 (21)	19/90 (21)	21/98 (21)
Maintenance	16/77 (21)	10/80 (13)	9/74 (12)	9/65 (14)
Urine protein albumin				
Baseline	18/91 (20)	18/90 (20)	15/91 (16)	16/96 (17)
Titration	30/91 (33)	32/94 (34)	27/90 (30)	35/98 (36)
Maintenance	23/77 (30)	20/80 (25)	14/74 (19)	15/65 (23)
Urine red blood cells				
Baseline	13/91 (14)	12/90 (13)	11/90 (12)	16/96 (17)
Titration	26/90 (29)	21/93 (23)	26/90 (29)	26/97 (27)
Maintenance	18/76 (24)	7/79 (9)	14/74 (19)	11/65 (17)
Urine sugar (glucose)				
Baseline	0/91	1/90 (1)	1/91 (1)	2/96 (2)
Titration	1/91 (1)	9/94 (10)	4/90 (4)	4/98 (4)
Maintenance	1/77 (1)	2/80 (3)	2/74 (3)	3/65 (5)
Urine uric acid crystals ^b				
Titration	1/1 (100)	1/1 (100)	3/3 (100)	2/2 (100)
Maintenance	3/4 (75)	2/5 (40)	2/3 (67)	2/5 (40)

^a N = number of patients with a test result, n = number with an abnormal test result of potential clinical importance.

Note: Baseline is not shown if all treatment group results were = 0

^b Uric acid crystals and urine calcium oxalate crystals were not defined in the protocol (see Table 9-8, Criteria for Determining Potentially Clinically Important Changes in Laboratory Test Results) however results fitting this criteria were reported.

This table was not in the original CSR.

Source: Table 6-5L-PCI (Section 14.3.4)

- One patient in this study experienced renal colic due to urolithiasis (Patient 0125 in the 300mg TID group). This 39 y/o male started therapy on 11/24/1999 and AE started on (b) (6). During participation in the Retigabine protocol, the patient was noted to have back pain and left hydronephrosis due to an obstructing distal ureteral calculus. Urolithiasis was surgically treated, with stone fragment identified as calcium oxalate monohydrate.

Study 301

- 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.

- The primary objective was to demonstrate a superior change in total partial seizure frequency per 4 weeks from baseline to the double-blind period (titration through maintenance) in patients treated with retigabine dosed at 1200 mg/day, in 3 equally divided doses, compared with placebo.
- The study consisted of an 8-week baseline phase to evaluate seizure frequency; a 6-week titration phase; and a 12-week maintenance phase. During the titration phase, patients were titrated from 300 mg/day to 1200 mg/day (400 mg TID) on blinded study drug.
- Patients who successfully completed the maintenance phase were invited to participate in an open-label extension study VRX-RET-E22-303. If they chose to do so, they entered the 6-week transition phase, during which the daily dose of retigabine for patients on active treatment remained at 1200 mg/day (400 mg TID), or, in the case of placebo patients, was titrated toward a target dose of 1200 mg/day (400 mg TID) in a double-dummy, double-blind manner.
- A total of 153 retigabine and 152 placebo patients aged 18 to 75 were included in the Safety Population. The average days on study drug were 97 days for retigabine and 114 days for placebo.
- Two treatment-emergent deaths (1 in each of the treatment groups) were reported. In addition there was one death that occurred 121 days after the patient took her last dose of study drug:

Patient 02805 in placebo group was a 57 y/o female who began treatment on 2/6/2007 and expired on (b) (6). Clinical history was consistent with traumatic injury with pneumothorax and anoxic brain injury as a terminal event.

Patient 02513 in Retigabine group was a 57 y/o male who began treatment on 12/28/2006 and expired on (b) (6). Clinical history and postmortem examination was consistent with diabetic ketoacidosis as a terminal event.

Patient 02703 in Retigabine group was a 26 y/o female who began treatment on 9/20/2006 and was withdrawn from study on 2/26/2007 due to a positive pregnancy test. The patient elected to abort the pregnancy on 07 Mar 2007. On 08 Jun 2007, the patient was reported to be missing. She was found dead in a well on (b) (6) after her last dose of study drug.

- For the SOC of renal and urinary disorders, TEAEs for patients in the retigabine group were 23% vs 7% for the placebo group. More patients in the retigabine group versus the placebo group reported AEs in the preferred term categories of urinary tract infection (12% vs 9%), urinary hesitation (5.9% vs 0.7%), and dysuria (5.2% vs 1.3%).

Table 8. Renal and Urinary Disorder Adverse Events Reported by 2 or More Patients in Either Treatment Group During the Double-blind Phase (titration and maintenance periods)

System organ class	Number (%) of patients	
	Placebo (N=152)	RTG 400 mg TID ^a (N=153)
Any renal and urinary disorder adverse event	10 (6.6)	35 (22.9)
Urinary hesitation	1 (0.7)	9 (5.9)
Dysuria	2 (1.3)	8 (5.2)
Chromaturia	0	7 (4.6)
Polyuria	1 (0.7)	4 (2.6)
Nephrolithiasis	0	4 (2.6)
Haematuria	1 (0.7)	2 (1.3)
Urinary retention	2 (1.3)	1 (0.7)

^a Adverse events are presented in descending order of incidence in the retigabine group.

RTG = retigabine, TID = three times daily

- All events related to voiding dysfunction were mild or moderate in severity. During the double-blind phase, there were no SAEs, dose reduction, or discontinuations due to voiding dysfunction in the retigabine group.

Patient 02508 had a preferred term AE of urinary retention which did not require any intervention. Mild clinical symptoms of urinary retention resolved and patient continued treatment with retigabine.

There was one patient in the placebo group (Patient 03901) a 58 y/o male who had a SAE of urinary retention during the transition period onto retigabine treatment for the open label extension study. On Jun 12 2007 (Day 127), the patient began blinded transition to retigabine. The patient experienced severe oliguria beginning 28 Jun 2007 (Day 143) and mild abdominal pain on 02 Jul 2007 (Day 147). On 09 Jul 2007, he was taking retigabine 250 mg TID and an interim PVR ultrasound revealed a prevoid volume of 2187 mL and a postvoid residual of 572 mL. Patient was discontinued from retigabine treatment on July 13, 2007. On 16 Jul 2007, three days after his last dose of study drug, the patient's prevoid volume was 162 mL with a postvoid residual volume of 0 mL. During a follow-up phone call on 13 Aug 2007, the patient reported no urinary complaints.

There was one additional patient in the placebo group (Patient 00103) a 20 y/o female who had a SAE of hematuria during the transition period onto retigabine treatment. This patient started the transition to retigabine dosing on 8/8/2006 (day 128). On (b) (6), while taking retigabine 350 mg TID, the patient was noted to have left flank pain, hematuria, and voiding difficulties requiring hospitalization. CT revealed bilateral

hydroureteronephrosis that was more prominent on the left. Patient symptoms and hydronephrosis resolved partially and was discharged on (b) (6) and continued in the study. This patient had an additional SAE during the safety extension Study 303 (see below).

- Notable in Study 301, four patients had listed AEs of nephrolithiasis in the retigabine treatment group vs none in the placebo group.

Table 9. The proportion of patients with urinary sediment / crystals at the end of maintenance period in Study 301

parameter	placebo	Retigabine 1200 mg/day
Amorphous crystals	0/119	3/87 (3.4%)
Amorphous phosphates	1/119 (0.8%)	1/87 (1.1%)
Amorphous urates	7/119 (5.9%)	12/87 (13.8%)
Calcium oxalate	4/119 (3.4%)	6/87 (6.9%)
Uric acid	2/119 (1.7%)	7/87 (8%)
pH (mean; change from baseline)	5.88 ; -0.08	5.67 ; -0.23

Subject 00302, a 32 y/o male began taking blinded retigabine on 03 June 2006 and reached maintenance phase of the study on 20 July 2006. While on retigabine 950 mg/day, patient reported passing a kidney stone on 06 Sept 2006. The event was assessed as resolved on the same day and the patient continued in the study.

Subject 00901, a 38 y/o male with history of urolithiasis began taking retigabine on 05 Jan 2006 and entered maintenance phase on 15 Feb 2006. While on retigabine 1050 mg/day, patient reported back pain on 25 Feb 2006 and was diagnosed with kidney stones on 01 March 2006. The event was reported as resolved on 12 April 2006 and patient continued in the study.

Subject 20210, a 37 y/o female began taking retigabine on 02 Dec 2006. On 13 Jan 2007 (day 43), patient discontinued study medication due to CNS related AEs. At the final study visit on 19 Jan 2007, patient reported renal lithiasis of mild intensity.

Subject 20221, a 36 y/o male began taking retigabine on 12 June 2007 and entered the maintenance phase on 23 July 2007. While on retigabine 1200 mg/day, patient reported mild nephric lithiasis on 20 Aug 2007. The patient

continued in the study without interruption and the event resolved on 15 October 2007.

Study VRX-RET-E22-303

- An open-label long-term extension of Study 301. Patients who completed the transition phase of Study 301 were to begin the open-label extension at a target dose of 1200 mg/day on the day following eligibility assessment. Patients who did not tolerate their final dose during transition phase could begin the open-label extension at a lower dose of retigabine. During Study 303, the investigator could modify the dose of retigabine or other AEDs to optimize patient response and tolerance.
- Interim data was submitted with a median time on open-label treatment for all patients of 357 days. Patients randomized to placebo in Study 301 began open-label treatment with approximately 6 weeks of prior retigabine exposure while patients randomized to retigabine had approximately 24 weeks of prior retigabine exposure. 79 patients had discontinued and 102 patients remained in the study (N=181). Primary reason for discontinuation include unsatisfactory response (30 patients), adverse event (24 patients), unwilling to continue (7 patients), non-compliance (6 patients) and failure to return (4 patients).
- 12% of patients had TEAEs noted in the SOC of renal and urinary disorders. 4 (2.2%) subjects had the preferred term AE of urinary retention that was mild, 3 (1.7%) patients had urinary retention that was moderate, and 1 (0.6%) patient had urinary retention that was severe in intensity and required discontinuation.

Table 10. Renal and Urinary Disorder Treatment-Emergent Adverse Events Reported by Two or More Patients During the Open-Label Extension Period

Preferred term ^a	Number (%) of Patients	
	(N=181)	
Any renal and urinary disorder adverse event	22	(12.2)
Urinary retention	8	(4.4)
Dysuria	4	(2.2)
Urinary hesitation	3	(1.7)
Bladder spasm	2	(1.1)
Nephrolithiasis	2	(1.1)
Pollakiuria	2	(1.1)
Urinary incontinence	2	(1.1)

^a Adverse events are presented in descending order of incidence.

Source: [Table 15](#) (Section 14.3.1)

- Case narratives of SAEs of urinary retention were reviewed:

Patient 00103, a 21 y/o female who had an SAE listed in Study 301 (noted above) had an additional SAE during this extension study, which required hospitalization on (b) (6). The hospital admission was precipitated by seizures, confusion, fever, and UTI. Overall, this patient's renal and urinary SAEs consists of voiding dysfunction, UTI, hematuria, and hydronephrosis.

Patient 00902, a 39 y/o male who had initially been randomized to the 400 mg TID group on 4/6/2006 and began treatment on the open-label extension study on 9/20/2006. Pt required hospitalization on (b) (6) for postictal psychosis and urinary retention while on retigabine dose of 300 mg TID. On 04 Mar 2008 (Day 699), a urology consult was obtained and a bladder scan revealed PVR urine volume of 700 cc and a foley catheter was placed. This urinary retention episode was reported to be resolved on 11 Mar 2008 (Day 706). On (b) (6) he was admitted to the hospital due to flurry of seizures and urinary retention. The patient was catheterized on (b) (6) and 990 cc of urine was collected and the patient was started on flomax 0.4 mg. This episode of urinary retention was reported to be resolved on 8/27/2008 and patient remained in study on treatment.

Patient 3505, a 30 y/o male who had initially been randomized to placebo began retigabine open label treatment on 1/9/2008 at 400 mg TID. On (b) (6) the patient was sent to the emergency room (ER) and was admitted to the hospital for observation over night due to psychomotor agitation, urinary retention and upper respiratory infection. A Foley catheter was inserted in the ER and 1200 cc of urine was evacuated. Study drug was reduced to 1050 mg/day on 23 Jan 2008 (Day 55) and stopped on 20 Feb 2008 (Day 83). Urodynamic study demonstrated a neurogenic bladder. At a follow-up visit to the urology clinic on 05 May 2008 (Day 158), the patient reported improvement and PVR in the office revealed 91 cc of residual urine. On 03 Jun 2008 (Day 187), the patient reported improved symptoms and the ability to spontaneously void and was self catheterizing less frequently.

- A report characterizing the urinary crystals in three human samples from Study 303 was submitted on July 2008 titled "Isolation and Characterization of Unknown Solid in Human Urine Sample from Valeant." Mass spectrometry evaluation of the unknown crystals identified peaks corresponding to the know molecular weight of retigabine and retigabine dimers.

Study 302

- 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 [300 mg/tid] and 600 mg/day [200 mg tid] used as adjunctive therapy in refractory epilepsy patients with partial-onset seizures.
- The primary objective was to demonstrate a superior change in total partial seizure frequency per 4 weeks from baseline to the double-blind period (titration through maintenance) in patients treated with retigabine dosed at 900 mg/day, in 3 equally divided doses (300 mg tid), compared with placebo.
- The study consisted of an 8-week baseline phase to evaluate seizure frequency; a 4-week titration phase; a 12-week maintenance phase. During the titration phase, patients were titrated from 300 mg/day to 600 or 900 mg/day with weekly increases in dose of 150 mg/day over the course of 2 to 4 weeks.
- Patients who successfully completed the maintenance phase were invited to participate in an open-label extension study VRX-RET-E22-304. If they chose to do so, they entered the 4-week transition phase, during which the daily dose of retigabine for patients on active treatment remained at 900 or 600 mg/day, or, in the case of placebo patients, was titrated toward a target dose of 900 mg/day (300 mg TID) in a double-dummy, double-blind manner.
- A total of 179 placebo, 181 retigabine 600 mg, 178 retigabine 900 mg patients aged 18 to 75 were included in the Safety Population. 85.5% of the placebo group, 74.6% of the 600 mg/day group, and 67.6% of the 900mg/day group completed the double-blind treatment phase.

Table 11. Renal and Urinary Disorder Adverse Events Reported by 2 or More Patients in Any Treatment Group During the Double-blind Phase – Safety Population

System organ class	Number (%) of patients					
	Placebo (N=179)		RTG 200 mg TID (N=181)		RTG 300 mg TID (N=178)	
Any renal and urinary disorder event	14	(7.8)	23	(12.7)	15	(8.4)
Dysuria	0		3	(1.7)	4	(2.2)
Urinary retention	0		1	(0.6)	4	(2.2)
Haematuria	2	(1.1)	5	(2.8)	2	(1.1)
Polyuria	4	(2.2)	1	(0.6)	2	(1.1)
Chromaturia	1	(0.6)	1	(0.6)	2	(1.1)
Urinary hesitation	3	(1.7)	6	(3.3)	1	(0.6)
Proteinuria	3	(1.7)	2	(1.1)	0	
Leukocyturia	2	(1.1)	2	(1.1)	0	
Micturition frequency decreased	1	(0.6)	2	(1.1)	0	
Urine flow decreased	2	(1.1)	1	(0.6)	0	
Crystalluria	0		2	(1.1)	0	

Adverse events are presented in descending order of incidence in the retigabine 300 mg TID group.

RTG = retigabine.

Source: [Table 12.2.9.1](#) (Section 14.3.1)

- 14 female and 8 male patients listed below had voiding dysfunction listed in the renal and urinary disorders SOC during the double blind treatment phase.

Table 12. Details of Adverse Events Related to Urinary Retention by Study Phase

Patient number	Preferred term	Start Day (Duration)	PVR (mL) at BL, W8, W16, Term	Severity	Action ^a	Related	SAE
Retigabine 300 mg TID (900 mg/day) – double-blind phase							
25108	Urinary retention	19 (39)	0, 1, 2, --	Mild	None	Possible	Yes
25215	Urinary retention	56 (Ongoing)	30, 156, 83, --	Mild	None	Possible	No
25405	Atonic urinary bladder	21 (140)	29, 159, 83, --	Moderate	Disc	Probable	Yes
30301	Urinary retention	29 (14)	38, --, --, 101	Severe	Disc	Probable	No
40119	Residual urine volume	114 (Ongoing)	115, --, 246, --	Mild	None	Possible	No
40701	Residual urine volume	58 (57)	31, 150, 40, --	Moderate	None	Possible	No
50102	Residual urine volume	57 (Ongoing)	7, 60, 180, --	Severe	None	Possible	No
50606	Residual urine volume	35 (Ongoing)	11, --, --, 65	Mild	None	Not related	No
60214	Urinary retention	32 (Ongoing)	30, --, --, --	Mild	None	Probable	No
80404	Urinary hesitation	33 (1)	140, 25, 55, --	Mild	None	Possible	No

Retigabine 200 mg TID (600 mg/day) – double-blind phase							
25407	Urinary retention	41 (44)	33, 28, 7, --	Mild	None	Possible	No
25411	Urinary hesitation	25 (33 – 64)	32, --, --, 10	Mild	None	Possible	No
40602	Micturition disorder	15 (Ongoing)	6, 15, 25, --	Mild	None	Possible	No
60210	Urinary hesitation	16 (95)	16, 12, 0, --	Mild	None	Probable	No
60215	Urinary hesitation	89 (38)	0, --, --, --	Mild	None	Probable	No
	Micturition freq decr	89 (38)		Mild	None	Probable	No
60402	Urinary hesitation	21 (3)	5, 9, 0, 10 ^b	Mild	None	Possible	No
	Urinary hesitation	51 (3)		Mild	None	Possible	No
60410	Urine flow decreased	14 (16)	0, --, --, 0	Mild	None	Possible	No
60501	Micturition freq decr	10 (32)	15, --, --, 33	Mild	None	Possible	No
60510	Urinary hesitation	53 (19)	25, --, 48, --	Mild	None	Possible	No
60601	Hypertonic bladder	49 (72)	7, 143, 0, --	Mild	None	Possible	No
60604	Bladder disorder	56 (Ongoing)	0, 88, 270, --	Mild	None	Possible	No
80304	Urinary hesitation	27 (Ongoing)	120, 660, --, --	Mild	None	Probable	No

- Two renal and urinary disorder AEs were reported as a SAE.

Patient 25108, a 31 y/o female had clinical complaints of voiding dysfunction on day 19 of the titration phase onto retigabine 300 mg TID treatment. PVR at various times were minimal and patient continued in the study with resolution of symptoms.

Patient 25405, a 34 y/o female, had voiding dysfunction with mildly elevated PVR of 159 and 83cc. Patient was discontinued from study with resolution of voiding dysfunction.

- Two additional patients had severe AEs in the SOC of renal and urinary disorders.

Patient 30301 had a preferred term AE of urinary retention. Patient was a 47 y/o female randomized to retigabine 300 mg TID on 18 Oct 2006. On 15 Nov 2006 (Day 29) patient reported severe symptoms of straining to urinate and began tapering off of study drug (PVR=101cc).

Patient 50102, a 47 y/o female had a preferred term AE of residual urine volume. Patient began treatment on 22 June 2006 with a baseline PVR of 7 ml. On 17 Aug 2006 patient had PVR of 60 ml, on 11 Oct 2006 a PVR of 180 ml, and on 06 Dec 2006 a PVR of 200 ml. Patient had no complaints of voiding dysfunction and continued in the study.

- Three additional patients had ongoing AEs related to increased PVRs.

Patient 40119, a 57 y/o female began taking retigabine on 19 Dec 2006 with a PVR of 115 ml. While on retigabine 900 mg/day on 11 April 2007 patient was noted to have a PVR of 246 ml with complaints of voiding dysfunction. There was no dose modification and patient continued in the study.

Patient 60604, a 18 y/o female began taking retigabine on 18 July 2006 with a baseline PVR of 0 ml. On 08 Nov 2006 patient was noted to have PVR of 270 ml without complaints of voiding dysfunction. Patient continued in the study without dose reduction and completed the study. Patient took the last dose of study medication on 05 Mar 2007 and the last PVR performed on 08 June 2007 noted a PVR of 8 ml.

Pt 80304, a 56 y/o male began taking retigabine on 01 Sept 2006 with a baseline PVR of 120 ml. Patient reported voiding dysfunction on 27 Sept 2006 and a PVR of 660 ml was noted on 12 Oct 2006 and a PVR of 375 ml on 10 May 2007. Pt had persistent voiding dysfunction but remained on retigabine 600 mg/day and completed the study.

- No AEs of nephrolithiasis were reported in this study.

Table 13. The proportion of patients with urinary sediment / crystals at the end of maintenance period in Study 302

<u>parameter</u>	<u>placebo</u>	<u>600 mg/day</u>	<u>900 mg/day</u>
Amorphous crystals	18/141 (12.8%)	24/126 (19%)	30/116 (25.9%)
Amorphous phosphates	1/141 (0.7%)	0/126 (0%)	1/116 (0.9%)
Amorphous urates	6/141 (4.3%)	5/126 (4%)	8/116 (6.9%)
Calcium oxalate	8/141 (5.7%)	7/126 (5.6%)	11/116 (9.5%)
Uric Acid	1/141 (0.7%)	7/126 (5.6%)	2/126 (1.7%)
pH (mean; change from	5.83 ; -0.16	5.74 ; -0.14	5.63 ; -0.23

baseline)			

Chong M. Kim, MD/PhD
Medical Officer
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
FDA/HHS/USA

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

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

/s/

CHONG M KIM
02/24/2010

MARK S HIRSCH
02/24/2010
I concur.

GEORGE S BENSON
02/24/2010

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	22345
Brand Name	Potiga ®
Generic Name	Retigabine
Sponsor	Valeant Pharmaceuticals
Indication	Adjunctive therapy in refractory epilepsy patients with partial-onset seizures
Dosage Form	Tablets
Drug Class	Partial onset-seizures
Therapeutic Dosing Regimen	200 mg TID, 300mg TID, 400 mg TID
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1200 mg/day (400 mg TID)
Submission Number and Date	30 Oct 2009 (SDN 001)
Clinical Division	DNP / HFD 120

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The sponsor used QTcI as their primary correction method. Based on our evaluation for different correction methods, we believe QTcF corrects RR more sufficiently than QTcI in this study; therefore, FDA analysis results based on QTcF are suggested for the labeling.

In this randomized, double-blinded (except for the use of moxifloxacin), active and placebo controlled, 3-arm parallel study, 120 healthy subjects received retigabine, placebo, or moxifloxacin. Overall summary of findings is presented in Table 1. The largest upper bounds of the 2-sided 90% CI for the mean difference between retigabine 400 mg and placebo was above 10 ms. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms; however, the moxifloxacin profile is missing the rising phase (Figure 4). To evaluate assay sensitivity, we would like to obtain moxifloxacin induced $\Delta\Delta\text{QTcF}$ effect at 15 minutes and 30 minutes post-dose.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Retigabine (400 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hrs)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
Retigabine (400 mg)	3	7.7	(3.5, 11.9)
Moxifloxacin 400 mg	1	13.1	(8.5, 17.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.1 ms.

The QTc prolongation risk of retigabine was evaluated under the highest titratable dose for healthy subjects (aimed 400 mg tid) over a 21-day period in the TQT study. Supratherapeutic dose is not included in this study due to tolerability issues. The exposures in the TQT study is lower than those that will occur in a clinical setting due to intrinsic factors (e.g., renal and hepatic impairment could cause 27-43% increase in C_{max} and about 100% increase in AUC) influencing retigabine exposure. To address these concerns, additional QTc data were collected in the Phase 3 clinical trials (VR-RET-E22-301, VR-RET-E22-302), in epilepsy patients up to 1200 mg/day (400 mg TID), and the studies planned to include patients with renal and hepatic impairment. In addition, ECGs are also being collected in the ongoing open-label extension studies to study 301 and 302 (Studies VR-RET-E22-303 and VR-RET-E22-304). The ECG results of these Phase 3 studies need to be reviewed.

1.2 QT-IRT COMMENTS

The following comments should be conveyed to the sponsor:

1. The moxifloxacin profile is not what we expected. The rising phase is missing. The maximum moxifloxacin induced $\Delta\Delta QTcF$ 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.

2 LABEL

2.1 SPONSOR'S PROPOSED LABEL AND QT-IRT RECOMMENDATIONS

We have used red-strike out for suggested text to be deleted and blue font for text to be included. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division

5.2 QT Interval Effect

A study of cardiac conduction demonstrated that retigabine produced a ~~slight and transient~~ QT-prolonging effect in healthy volunteers titrated to ~~1,200~~ 400 mg/day ~~TID~~. The QT-prolonging effect occurred within 3 hours of dosing ~~at 1,200 mg~~. ~~Caution should be exercised~~ Monitor the QT frequency when POTIGA is prescribed with medicines known to increase QT interval and in patients with congenital long QT syndrome, heart

failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia [See also in Section 12.2]

12.2 Pharmacodynamics

In a randomized, double-blind, active- and placebo-controlled parallel-group study, 120 healthy subjects (40 in each group) were administered POTIGA titrated up to the final dose of 400 mg 3 times daily, placebo, and placebo and moxifloxacin (on day 22). After 22 days of dosing, the maximum mean (upper 1-sided, 95% CI) increase of baseline and placebo adjusted QTc interval based on Fridericia correction method (QTcF) was ~~individually corrected QT interval~~ 7.7 ms (11.9 ms) ~~(QTcI) was 5 ms (10.3 msec)~~ and was observed at 3 hours after dosing. The QTc prolongation risk of retigabine was evaluated under the highest titratable dose for healthy subjects. However, the dose tested in the trial is not sufficient to provide adequate safety margins to cover potential exposure increases due to renal or hepatic impairment. ~~In a post hoc analysis of subjects who reached the dose of 400 mg 3 times daily, the maximum mean (upper 1-sided 95% CI) increase of baseline and placebo adjusted QTcI was 6.7 ms (12.6 msec). The effect was transient and limited to the first 3 hours after dose.~~ No effects on heart rate, PR, or QRS intervals were noted. Caution should be exercised when retigabine is prescribed with medicines known to increase QT interval and in patients with congenital long QT syndrome, congestive cardiac failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia [see Warnings and Precautions (5.2)]

17.2 QT Interval Effect

Patients should be advised that POTIGA is associated with electrocardiographic changes that could lead to ~~irregular heart beats~~ changes in heart rhythm that could be life-threatening, especially in patients taking other medications known to increase the QT interval and in patients with congenital long QT syndrome, heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia [see Warnings and Precautions (5.2)].

3 BACKGROUND

Retigabine (RTG), is a first in class neuronal potassium channel opener for the treatment of partial-onset seizures. Within this application, retigabine is also referred to by the laboratory designations of GKE-841, D-23129, WAY-143841, and GW582892.

3.1 MARKET APPROVAL STATUS

Retigabine is not approved for marketing in the USA or elsewhere.

3.2 PRECLINICAL INFORMATION

Source Non-Clinical Overview- eCTD Module 2.4

“In vitro, RTG reduced the amplitude of the KCNQ1/KCNE1 mediated cardiac K⁺ conductance by channels transiently expressed in CHO cells. The IC₅₀ for this effect was approximately 100 μM (~30,000 ng/mL). RTG also minimally inhibited hERG-mediated inward tail currents with an IC₅₀ of approximately 100 μM (m2.6.3.4, Report D-23129/FP1-05/00). These results were similar to those

reported by Tatulian (2001) who demonstrated that the RTG IC₅₀ of KCNQ1/KCNE1 channel activation was 100.1 μ M in CHO cells. RTG was a partial inhibitor, producing only 65% inhibition of KCNQ1/KCNE1 at a concentration of 1000 μ M. These IC₅₀ values represent approximately 20 times the expected peak concentrations at the highest clinical therapeutic dose of 1200 mg (mean C_{max} of approximately 1520 ng/mL) or approximately 100-fold the expected peak free drug plasma concentration. The N-acetyl metabolite (NAMR) IC₅₀ for hERG inhibition was greater than 1000 μ M (m2.6.3.4, Report PR2007-009), showing negligible inhibitory potential at relevant therapeutic doses.

“In the isolated Langendorff-perfused guinea pig heart model, RTG was without significant effect on the evaluated endpoints at concentrations of 1, 3 and 10 μ M (i.e. up to 3033 ng/mL), with all observed endpoints being within the range of those observed with vehicle control (m2.6.3.4, Report D-23129/FP-19/98). At concentrations of 30 and 100 μ M, a concentration-dependent reduction in heart rate of 19% and 47%, respectively was observed along with an increase in the PQ interval (16 and 29% respectively). RTG up to 30 μ M had no effect on the QRS or QT intervals, however, at 100 μ M [30, 330 ng/mL; a concentration that is ~20 times the expected maximum clinical RTG plasma concentration at 1200 mg/day (1520 ng/mL)] a 17% increase in the duration of the QT interval was observed (m2.6.3.4, Report D-23129/FP-19/98). NAMR (1, 3 and 10 μ M) had no effect on QT interval and QRS-interval at concentrations up to 10 μ M (m2.6.3.4, Report D-23129/FP-19/98).

“In vitro studies in cat myocytes demonstrated that RTG caused both a slight reduction in the rapid delayed rectifier current [I_{Kr}; (14% inhibition at 10 μ M)] and a slight reduction in the L-type Ca²⁺ current (I_{Ca-L}; 18% inhibition at 10 μ M), resulting in a net 15% shortening of the cardiac action potential duration (APD₉₅) at 95% of full polarization. Thus, the combined physiological effects of RTG on the ion channels did not lead to a lengthening of the QT interval. NAMR produced similar effects to those observed with RTG, although of lesser magnitude. The myocyte APD was further reduced at RTG and NAMR concentrations of 100 μ M. In dog Purkinje fibers in vitro, RTG at 10 μ M had no effect on APD at 50% of full repolarization; however, at the higher concentration of 100 μ M, it caused shortening of the APD₅₀. The results are consistent with the effect of blocking of the I_{Ca-L} current, and do not appear to be suggestive of an RTG-induced lengthening of APD and/or QT_c at therapeutic doses

“No effects on electrocardiograms (ECG) were reported in CV/respiratory safety pharmacology studies conducted in dogs. In a pilot study, conscious dogs were administered cumulative i.v. doses of up to 8 mg/kg RTG (25 minute infusion per dose). There was no effect on ECG parameters and no arrhythmias were recorded even at doses causing overt clinical signs including hyperexcitability and vomiting (m2.6.3.4, Report D-23129/FP-11/99). RTG had no effect on ECG parameters (including corrected QT interval) monitored continuously by telemetry in conscious, unrestrained Beagle dogs given daily oral (capsules) doses of 5, 18

or 38 mg/kg for 7 days. However, statistically significant decreases in mean heart rate (18-42% without a clear dose relationship) and dose-related decreases (9-21%) in mean arterial blood pressure were noted at ≥ 5 mg/kg/day (m2.6.3.4, Report D-23129/9321020108).

“In addition to the ECG investigations performed during the safety pharmacology CVS studies, ECG investigations were also performed in multiple long-term toxicity studies in Beagle dogs using RTG and NAMR. In brief, there were no ECG effects observed following RTG administration in the multiple dog studies of 2-52 weeks duration (AUC (0.5-24) values for RTG reached approximately 8300-25300 ng·hr/mL in the 52 week dog study) or NAMR administration in a 13- week dog study (where C_{max} and AUC (0-24) values for NAMR reached 12300-13100 ng/mL and 36400-55900 ng·hr/mL respectively for the top dose of 100 mg/kg/day).”

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety, eCTD 2.7.4

“As of 31st December 2008, a total of 2034 subjects were exposed to at least 1 dose of retigabine in the epilepsy clinical development program

“As of 31st December 2008 there were 13 treatment-emergent deaths in the epilepsy clinical development program; 3/427 (0.7%) were patients who received placebo and 10/1365 (0.7%) patients who received retigabine.

“Cardiac AEs:

“Clinical Pharmacology Studies

Five subjects reported TESAEs, of which 3 were cardiac events.

- In Study VRX-RET-E22-108, 2 subjects reported a TESA (cardiac arrest/asystole and ventricular tachycardia) after a single 900mg dose of retigabine (CSR VRX-RET-E22-108, Section 12.3.2.1). There was no evidence from telemetry recordings that either SAE was associated with QT changes. Both events were considered to be at least possibly related to study drug by the investigator, and resulted in withdrawal from the study. Both subjects recovered without sequelae
- One subject in Study 3065A1-107 (CSR 3065A1-107, Section 9.3) reported a TESA (ventricular extrasystoles) after 600 mg RTG that was considered to be drug-related by the investigator and resulted in withdrawal from the study. Although not reported as an SAE in the CSR, this event has been classified as an SAE.

“All Phase II/III Combined

Cardiac rhythm/conduction abnormalities were reported for 8% of patients

Table 100 Cardiac Rhythm/Conduction Abnormalities Reported in at least 2 Patients (Safety Population: All Phase II/III Combined)

	Number (%) of Patients
Preferred Term	RTG (N=1365)
Any Event	111 (8.1)
Chest pain	38 (2.8)
Palpitations	18 (1.3)
Syncope	12 (0.9)
Chest Discomfort	6 (0.4)
ECG QT prolonged	4 (0.3)
Heart rate irregular	4 (0.3)
Tachycardia	3 (0.2)
Arrhythmia	2 (0.1)
AV Block first degree	2 (0.1)
AV Block second degree	2 (0.1)
Bradycardia	2 (0.1)
Sinus Bradycardia	2 (0.1)
Supraventricular tachycardia	2 (0.1)
Ventricular extrasystoles	2 (0.1)
ECG ST-T change	2 (0.1)
Heart rate increased	2 (0.1)
Loss of consciousness	2 (0.1)
Syncope vasovagal	2 (0.1)

Data Source: [Table 12.08](#)

“There were 7 SAEs: 5 of chest pain, 1 of syncope and 1 of arrhythmia/bradyarrhythmia with pauses in cardiac rhythm with an absence seizure. Patient 208-000001 described chest pain as intermittent, without any significant medical history. Patient 304-090503 had increased seizures and chest pain, however cardiac investigations found no abnormalities. Patient 302-090514 had underlying ECG changes that were unchanged from a historical ECG with all other cardiac investigations reported as normal. Syncope was an SAE in Patient 003101 from Study 301. Chest pain was the most common SAE however there was no clinical evidence of any new cardiac pathology.

“Increases in QTcB or QTcF in patients in the All Phase II/III Combined studies were broadly similar to those in the pivotal controlled trials (PCT) data set. However, interpretation of these data is limited by the small number of patients contributing data at later timepoints

Table 136 Findings for QTc of Potential Clinical Concern (Safety Population: All Phase II/III Combined)

	Number of Patients ² /Number of Patients Evaluable (%)
	RTG (N=1365)
QTc Bazett's	
Increase >30 msec from baseline	253/1213 (20.9)
Increase >30 msec and ≤60 msec from baseline	246/1213 (20.3)
Increase >60 msec from baseline	22/1213 (1.8)
Post-baseline ≥450 msec ¹	56/1213 (4.6)
Post-baseline ≥480 msec ¹	6/1213 (<1.0) ³
Post-baseline ≥500 msec ¹	1/1213 (<0.1) ⁴
QTc Fridericia's	
Increase >30 msec from baseline	198/1213 (16.3)
Increase >30 msec and ≤60 msec from baseline	196/1213 (16.2)
Increase >60 msec from baseline	12/1213 (1.0)
Post-baseline ≥450 msec ¹	18/1213 (1.5)
Post-baseline ≥480 msec ¹	3/1213 (<1.0) ⁵
Post-baseline ≥500 msec ¹	0

Data Source: [Table 15.11](#)

1. And baseline < this value or missing.
 2. A patient may be counted more than once, if they had ECG parameters that met different criteria across various timepoints.
 3. Three of these patients had PCC values at baseline ([Table 15.17](#)).
 4. This patient also had a PCC value at baseline ([Table 15.17](#)).
 5. One patient also had a high value at baseline ([Table 15.17](#)).
- Data are for any post-baseline finding.

Reviewer's Comments: Syncopal episodes were not reported to be associated with QT prolongation. Cardiac asytle and ventricular tachycardia have been reported as TEAEs but not associated with QT prolongation. On review of the deaths in the RTG group 7/10 are reported as possible or probable SUDEP (sudden unexplained death in epilepsy). Comparison to the background rate of SUDEP in patients with epilepsy is unavailable.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of retigabine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study. The sponsor submitted the study report *study-report-vrx-ret-e22-103.pdf* for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind Randomized Parallel-group Trial to Define the ECG Effects of Retigabine Using a Maximum Tolerated Dose Compared with Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough ECG Trial

4.2.2 Protocol Number

VRX-RET-E22-103

4.2.3 Study Dates

07 June 2007 to 10 October 2007

4.2.4 Objectives

Primary:

The primary objective of this study was to evaluate the effects of retigabine relative to placebo, on the time-matched change from baseline in the QT interval corrected for heart rate (QTc) using an individual formula (QTcI).

Secondary:

The secondary objectives of the study were:

- To evaluate the effects of retigabine on QT interval corrected using Fridericia's formula (QTcF) and the QT interval corrected using Bazett's formula (QTcB) (provided for historical reasons only);
- To evaluate the effects of retigabine on heart rate, PR interval, QRS interval, uncorrected QT interval, change in electrocardiogram (ECG) morphological patterns
- To evaluate the correlation between the QTcI change from baseline and plasma concentrations of the parent drug and metabolites
- To evaluate the safety and tolerability of retigabine

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, single-center, double-blind (except for the use of moxifloxacin), randomized, 3-arm parallel-group study in healthy male and female subjects. Subjects were randomly assigned (40 subjects per treatment group, evenly balanced by gender) to receive retigabine, placebo, or moxifloxacin. Subjects were confined to the Phase 1 unit from Day -1 until Day 23 (24 hours after the last dose).

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study was conducted in a double-blind fashion between retigabine and placebo. The positive control, moxifloxacin, was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

120 healthy subjects (40 subjects in each treatment arm; 20 female, 20 male) were randomized in this trial to receive one of the following 3 treatment regimens: placebo, moxifloxacin 400 mg, and the highest retigabine therapeutic dose (targeting 1200 mg/day) at steady state.

Subjects assigned to the retigabine group received 100 mg of retigabine 3 times a day (TID) on Day 1 through Day 3. Every 72 hours from Day 4 through Day 21, the retigabine dose was increased by 50 mg, reaching a maximum dose of 400 mg TID on Day 19 if the drug is tolerable. On the morning of Day 22, subjects received a single 400-mg dose of retigabine. Subjects assigned to the placebo group received placebo tablets TID on Days 1 through 21, and a single dose of placebo on the morning of Day 22. Subjects assigned to the moxifloxacin group received placebo on Days 1 through 21, and a single 400-mg moxifloxacin tablet on the morning of Day 22.

Table 1. Dosing Schedule

Days	Placebo Group			Moxifloxacin Group			Retigabine Group		
	8 AM	2 PM	10 PM	8 AM	2 PM	10 PM	8 AM	2 PM	10 PM
1–3	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	100 mg	100 mg	100 mg
4–6	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	150 mg	150 mg	150 mg
7–9	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	200 mg	200 mg	200 mg
10–12	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	250 mg	250 mg	250 mg
13–15	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	300 mg	300 mg	300 mg
16–18	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	350 mg	350 mg	350 mg
19–21	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	400 mg	400 mg	400 mg
22	Placebo			Moxi-floxacin			400 mg		

(Source: Sponsor’s Clinical Study Report, Table 9-1 on Page 26)

Reviewer’s Comment: Even with the slow titration schedule, about 1/3 of subjects assigned to the retigabine group failed to reach the highest dose of 1200 mg/day due to tolerability issues. Among them, 5 subjects reached a final dose of 750mg/day, 4 subjects reached 900 mg/day and 2 subjects reached 1050 mg/day.

4.2.6.2 Sponsor’s Justification for Doses

“The following important constraints guided the proposed study dose:

- In Study 205, the 900 mg/day and 1200 mg/day dose levels were statistically superior to placebo and are putative therapeutic doses. The 600 mg/day dose level showed a positive trend. Thus the highest known therapeutic dose level is 1200 mg/day.
- It was established that while human subjects may be able to tolerate single retigabine doses of 400 to 600 mg, the starting unit dose of 100 mg administered in a multiple-dose study would be best tolerated.
- In the phase III program patients are titrated from 300 mg/day to 1200 mg/day over a 42-day period.
- The sponsor received advice from Dr. Joel Morganoth (Valeant consultant) that thorough QTc studies be conducted with treatment durations of 21 days or less because of variability in the QT interval over time.
- The sponsor chose a titration strategy that aims to get subjects to 1200 mg/day by Day 19 of dosing in order to make the best attempt to assess the impact on the QT

interval, if any, of the highest known therapeutic dose of retigabine. Subjects will start at 300 mg/day (given tid) and go through a forced titration of 150 mg/day every 3 days.

- The forced titration approach would allow achieving steady state at each of the dose levels prior to escalation. Subjects who are unable to tolerate the titration will be asked to remain in study to run the end of study QT interval assessments at their individually-determined highest tolerated dose. Thus the informative data at the maximum tolerated dose (MTD) for each individual can be gathered.”

Reviewer’s Comment: Sponsor’s justification for the therapeutic dose of 1200 mg/day in the TQT study is acceptable. With the maximum tolerated dose achieved by forced titration over a 21-day period, the TQT study maximized QT prolongation risk information of retigabine and minimized the variability in the QT interval over time. Supratherapeutic dose is not plausible in this study. The exposures in the TQT study can be expected to be lower than those that will occur in a clinical setting due to intrinsic factors (e.g., renal and hepatic impairment could cause 27-43% increase in C_{max} and about 100% increase in AUC) influencing retigabine exposure if the exposure is tolerable in those patients. To address these concerns, additional QTc data were collected in the Phase 3 clinical trials in epilepsy patients up to 1200 mg/day (400 mg TID) dose, and this population can include patients with renal and hepatic impairment. The results of these Phase 3 studies need to be reviewed.

4.2.6.3 Instructions with Regard to Meals

All doses of the study drug were administered orally with 240 mL of water, with or without food according to the dosing schedule presented in Table 1. The Phase 1 unit ensured that the same meal timing and components as well as activity levels and general conditions were as close as possible at baseline (Day –1) and at steady state on Day 22.

Reviewer’s Comment: Acceptable. Administration of retigabine tablet with high fat meal increases C_{max} by 14 – 38% (appendix 6.1). In clinical practice, retigabine will be taken with or without food. The conduct of the trial reflects the clinical practice.

4.2.6.4 ECG and PK Assessments

- ECGs were obtained digitally using a Mortara Instrument (Milwaukee, WI) H-12 continuous 12-lead ECG recorder at baseline (Day –1) and then again on Day 22 at the following time points in all 3 treatment groups: before dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dosing. Seventy ECGs were analyzed at baseline and also on Day 22, resulting in a total of 140 ECGs in each of the 120 subjects, or an overall total of 16 800 ECGs. Any subject who was unable to tolerate the assigned treatment and wished to discontinue the study early was subjected to the ECG procedures planned for Day 22.
- To minimize the effect of phlebotomy on the comparisons of QT measurement, blood samples were collected at baseline from all subjects at times matching the pharmacokinetic blood sampling on Day 22. No analysis was performed on the

blood samples taken at baseline. Blood samples were also obtained before dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dosing. On Day 22, plasma samples for both retigabine and the N-acetyl metabolite of retigabine were obtained from all subjects on all treatments to maintain comparable study conditions and the blind, but were only analyzed for the active treatment groups.

Reviewer's Comment: The timings of the ECGs and the PK are acceptable. The sampling schedule is adequate to cover the T_{max} of the parent (or metabolite) compound and the potential delayed effect up to 24 hours.

4.2.6.5 Baseline

Time matched ECG measurements on Day -1 were used as baseline.

4.2.7 ECG Collection

ECGs were obtained digitally using a Mortara H-12 continuous 12-lead ECG recorder at the time points specified above. The ECGs were stored on a flash card about every 10 seconds and were not available for review until the card was received by the central ECG laboratory and analyzed. Five 12-lead ECGs were downloaded from the H-12 flash card within about 5 minutes (providing 5 ECGs for each time point).

All ECGs were read at the central ECG laboratory using a high-resolution manual on-screen caliper semiautomatic method with annotations.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

120 healthy male or female subjects 18-45 years of age with a normal baseline ECG and BMI between 19-28 kg/m² were randomized and 102 subjects completed the study. 16 subjects (14 in the RTG group) discontinued due to an adverse event. Of these 14 subjects in the RTG group, 2 subjects received up to 250 mg; 7 subjects received up to 300 mg; 4 subjects received up to 350 mg; and 1 subject received up to 400 mg.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

For the time-averaged analysis of ECG data, the change-from-baseline values were analyzed by a linear mixed model with gender and treatment as fixed factors and the baseline value as a covariate. The 90% CI was provided for the difference between the active treatments (retigabine and moxifloxacin) and placebo.

During the course of the study, not all subjects were able to tolerate the planned 1200-mg/day retigabine dose. Therefore, it was determined that ECG and PK analyses would be examined for 2 separate populations: the original analysis population (subjects with available ECG and PK data at baseline and after dosing) and a post-hoc subgroup "completer" population (subjects randomly assigned to the retigabine group who were able to complete the study). There are 26 completers out of 38 subjects in the retigabine group.

In the time-matched QTcI analysis for the ECG population including non-completers, the upper bound of the CI remained below 10 ms at all time points, with the exception of a single time point at 3 hours after dosing when the upper bound reached 10.3 ms (point estimate 5.0 ms).

The time-matched analysis for the ECG population demonstrated that the QTc endpoint for the moxifloxacin group met the assay sensitivity criteria outlined in the statistical plan, with the largest upper bound to be 5.6 ms at 1 hour after dose and a typical profile that is usually seen for this positive control agent.

4.2.8.2.2 Categorical Analysis

There is no observation with QTcI > 450 ms under any treatment. There were 5 subjects with Δ QTcI between 30 ms and 60 ms, 2 from retigabine group, 2 from moxifloxacin group and 1 from placebo. No subject had more than 25% increase of PR or QRS from baseline when PR > 200 ms or QRS > 100 ms.

4.2.8.2.3 Additional Analyses

For the completer ECG population, the time-matched placebo- and baseline-corrected QTcI data for the maximum dose of retigabine showed that all mean values were less than or equal to 5 ms except for Hour 2 (6.4 ms) and Hour 3 (6.7 ms). All upper CIs were less than 10 ms except for Hours 1, 2, and 3 where the upper CIs were 10.4 ms, 12.5 ms, and 12.6 ms, respectively. In the completer ECG population, 1 subject who received retigabine and placebo and 2 subjects who received moxifloxacin were observed to have the nonspecific outlier criterion of a 30 to 60 ms change from baseline in QTcI.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in the study

AEs leading to study discontinuation were as follows: headache, tremors, dyskinesia, labile affect, confusion, hallucinations, rash, feeling drunk, furuncle and myalgias.

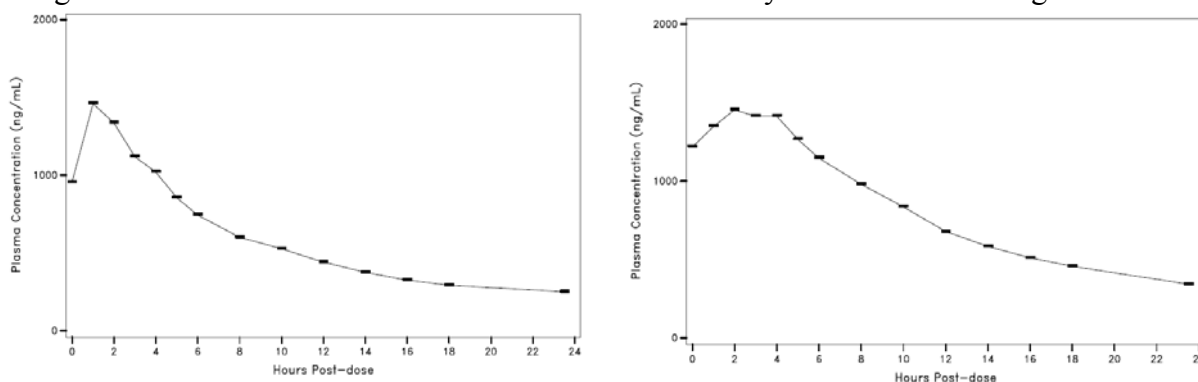
There were two cases of syncope reported as vasovagal in the retigabine and placebo groups. Narratives for this AE are unavailable.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean concentrations of retigabine and the N-acetyl metabolite of retigabine from the 26 completers with a final dose of 400 mg on day 22 are presented in Figure 1. Mean PK parameters are shown Table 2 and Table 3.

Figure 1: Mean Concentration-time Profiles of Retigabine (Left) and the N-acetyl Metabolite of Retigabine (Right): Completers with a Final Dose of 400 mg



(Source: Sponsor's Clinical Study Report, Figure 11-1/2 on Page 56/58)

Table 2: Summary of Plasma Pharmacokinetic Parameters for Retigabine

Parameter (unit)	Completer Pharmacokinetic Population (400 mg Q8H)		Overall Pharmacokinetic Population (all doses)	
	N	Arithmetic Mean (CV%)	N	Arithmetic Mean (CV%)
AUC _{0-8hr} (ng•h/mL)	26	7993.01 (37)	38	7514.38 (37)
C _{max} (ng/mL)	26	1501.20 (32)	38	1446.21 (30)
T _{max} ^a (h)	26	1.00 (1.00, 4.00)	38	1.00 (1.00, 4.00)
t _{1/2} (h)	15	10.12 (28)	22	10.35 (28)

^a Median (minimum, maximum)

(Source: Sponsor's Clinical Study Report, Table 11-3 on Page 57)

Table 3: Summary of Plasma Pharmacokinetic Parameters for the N-acetyl Metabolite of Retigabine

Parameter (unit)	Completer Pharmacokinetic Population (400 mg Q8H)		Overall Pharmacokinetic Population (all doses)	
	N	Arithmetic Mean (CV%)	N	Arithmetic Mean (CV%)
AUC _{0-8hr} (ng•h/mL)	26	10 215.02 (31)	38	9653.32 (32)
C _{max} (ng/mL)	26	1504.01 (31)	38	1423.47 (31)
T _{max} ^a (h)	26	2.00 (1.00, 4.00)	38	2.00 (0.00, 4.00)
t _{1/2} (h)	25	10.45 (27)	35	10.50 (28)

^a Median (minimum, maximum)

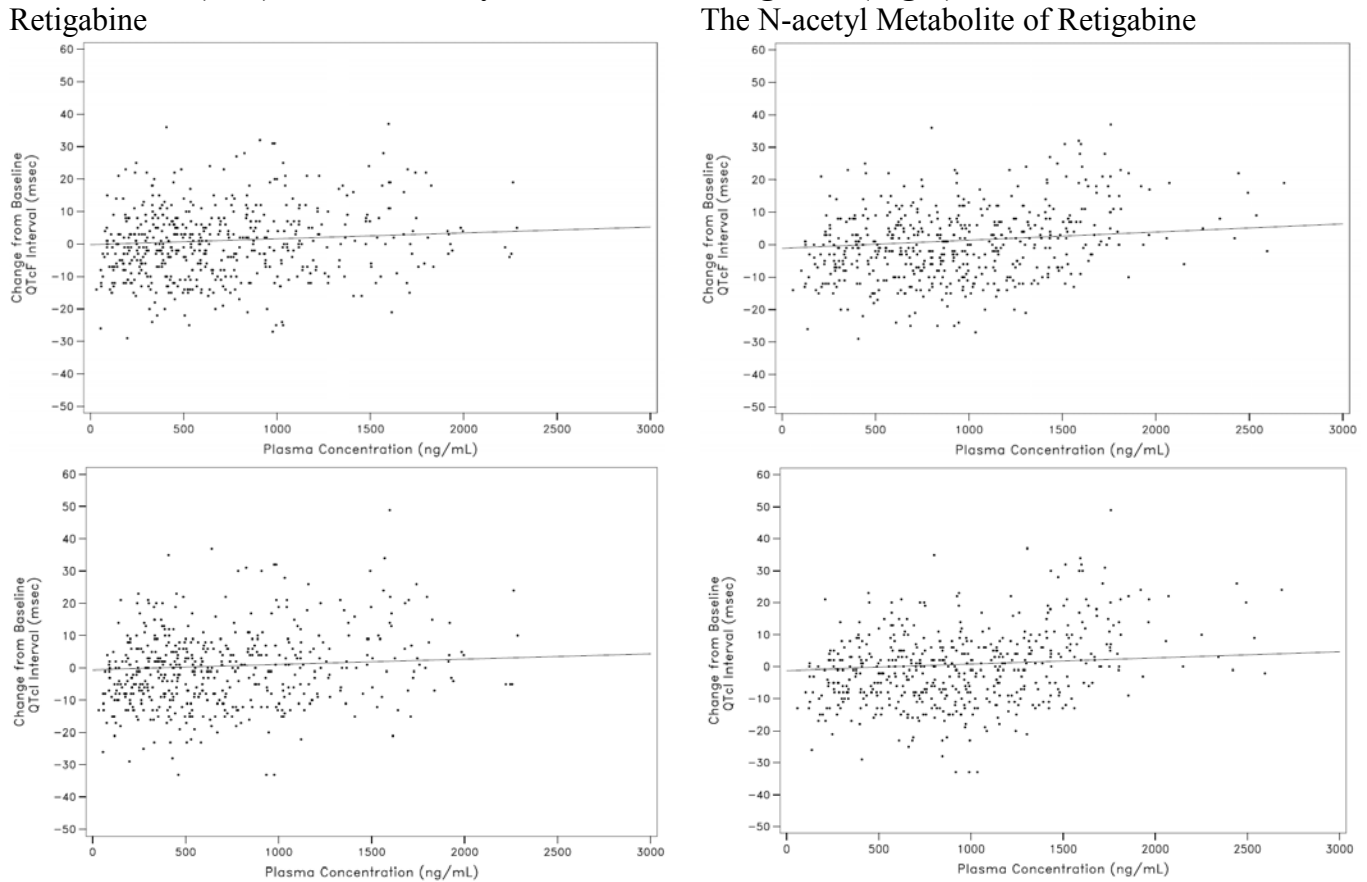
(Source: Sponsor's Clinical Study Report, Table 11-4 on Page 59)

Reviewer's Comments: The sampling schedule appears adequate to characterize the time course of retigabine and its N-acetyl metabolite.

4.2.8.4.2 Exposure-Response Analysis

The concentration-QT (pharmacokinetic-pharmacodynamic) model results showing the slopes of the relationships for the predicted QTcI change from baseline versus the retigabine and the N-acetyl metabolite of retigabine concentrations are shown in Table 4 and Figure 2. The model demonstrated statistically significant positive but relatively flat slopes.

Figure 2: Change (ms) from Baseline in QTcF (top) and QTcI (bottom) versus the Retigabine (Left) and the N-acetyl Metabolite of Retigabine (Right) Concentrations



(Source: Sponsor's Clinical Study Report, Figure 11-1/2 on Page 56/58)

Table 4: Change (ms) from Baseline in QTcI, QTcF, and QTcB versus the Retigabine (top) and the N-acetyl Metabolite of Retigabine (bottom) Concentrations - Estimates from Linear Mixed Model

PK-PD Analysis - Retigabine PK Population						
QTc Parameter (Change from Baseline)	Slope of Plasma Concentration	Standard Error of Slope	P-value of Slope	Predicted QTc (Change from Baseline) at Average Cmax	One-sided Upper 95% Confidence Bound [1]	Overall Model Fit [2]
QTcI	0.0017	0.00053	0.0032	1.81	4.271	<.0001
QTcF	0.0018	0.00056	0.0025	2.42	4.843	<.0001
QTcB	0.0026	0.00092	0.0071	1.50	5.016	<.0001
PK-PD Analysis - N-acetyl Retigabine PK Population						
QTc Parameter (Change from Baseline)	Slope of Plasma Concentration	Standard Error of Slope	P-value of Slope	Predicted QTc (Change from Baseline) at Average Cmax	One-sided Upper 95% Confidence Bound [1]	Overall Model Fit [2]
QTcI	0.0019	0.00055	0.0011	1.59	3.879	<.0001
QTcF	0.0025	0.00060	0.0002	2.44	4.724	<.0001
QTcB	0.0027	0.00087	0.0039	0.77	3.918	<.0001

Note: Repeated measure linear mixed models with plasma concentration as a fixed effect, and subject as a random effect were performed on the change from baseline values (not placebo-corrected).

[1] One-sided Upper 95% Confidence Bound of the Predicted QTc Parameter Change from Baseline at Average Cmax.

[2] Overall Model Fit: p-values from the likelihood ratio tests.

(Source: Sponsor's Clinical Study Report, Table 14.2.9-10 on Page 459 and 497)

Reviewer's Comments: The FDA reviewer performed independent analyses (see section 5.3). Consistent with the sponsor's results, the slope of the concentration-response relationship is significantly greater than 0, but relatively flat.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI) provided by the sponsor. We also evaluated the linear relationships between different correction methods (QTcB, QTcF, QTcI) and RR. The mixed model shows a smaller slope of QTcF vs. RR than that of QTcI vs. RR, which indicates that QTcF is a better correction method than QTcI for this study. We also looked at the Mean Sum of Squared Slopes (MSSS). The smaller this value is, the better the correction. Again, QTcF produces the smallest MSSS. Therefore, the FDA reviewer used QTcF for the primary statistical analysis. We performed QTc analysis based on both Fridericia and individual correction methods and found that the results were similar.

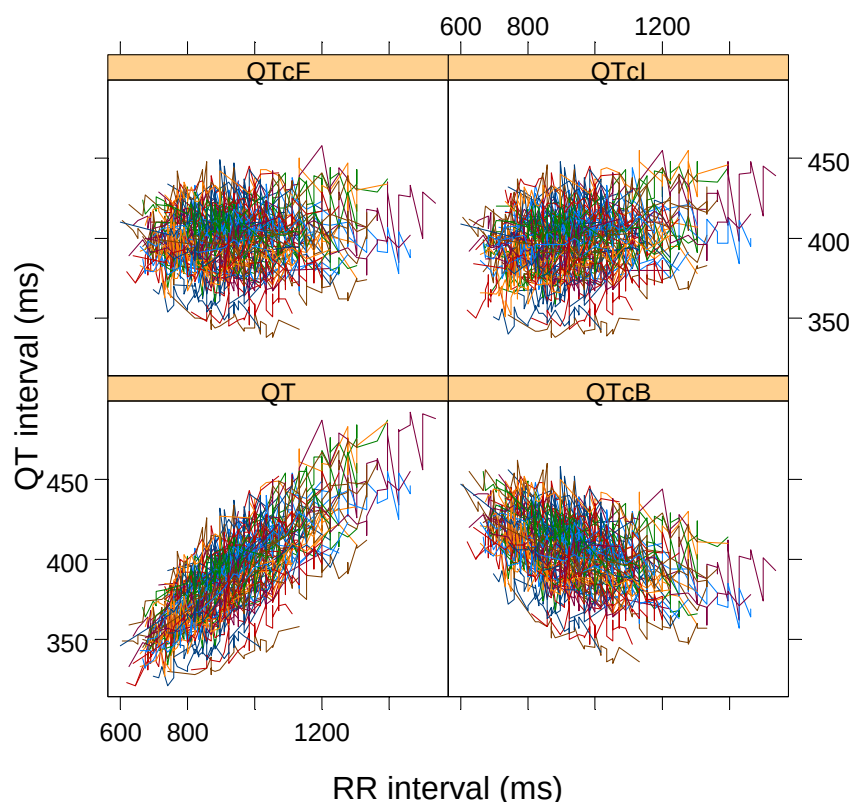
Table 2: Mixed Model Comparison of QTcF and QTcI

Treatment Groups	Slope of QTcF	Slope of QTcI	diff_p_value
Moxifloxacin	0.016	0.035	< 0.001
Overall	0.0083	0.024	< 0.001
Placebo	0.012	0.020	0.01
Retigabine	-.00004	0.020	< 0.001

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment							
	Moxifloxacin		Placebo		Retigabine		ALL	
method	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	38	0.0049	39	0.0051	38	0.0051	115	0.0050
QTcF	38	0.0013	39	0.0016	38	0.0008	115	0.0012
QTcI	38	0.0029	39	0.0021	38	0.0018	115	0.0023

Figure 3: QTcF, QTcI (from the sponsor), QT, and QTcB vs. RR (Each Subject's Data Points Are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Retigabine

During the course of the study, not all subjects were able to tolerate the planned 1200-mg/day retigabine dose. Only 26 out of 38 subjects reached the target dose (400 mg, BID) in the retigabine group. A total of 5 subjects reached a final dose of 750mg/day, 4 subjects reached 900 mg/day and 2 subjects reached 1050 mg/day. The statistical reviewer used all 38 subjects from retigabine group in the analysis including those who did not reach the final doses.

Time-matched 24 hour ECG at day -1 was used as baseline. The statistical reviewer used generalized linear model to analyze the $\Delta\Delta\text{QTcF}$ effect on day 22. The model includes treatment, gender and baseline QTcF as covariates. Model estimates LS means between different treatment groups and placebo and their 90% confidence intervals. The analysis results are listed in

Table 4. The results are from intent to treat analysis with all the ECG population including those who did not reach the final doses. The largest upper bound of the 2-sided 90% CI for the mean difference between retigabine and placebo were 11.9 ms at 3 hours after dose.

Table 4: Analysis Results of $\Delta QTcF$ and $\Delta\Delta QTcF$ for Treatment Groups of Retigabine

	Retigabine	Placebo	$\Delta\Delta QTcF$	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
1	-2.6	-4.8	2.2	(-2.5, 6.8)
2	3.1	-1.6	4.7	(0.4, 8.9)
3	5.8	-1.9	7.7	(3.5, 11.9)
4	0.7	-2.6	3.3	(-1.2, 7.7)
5	1.2	-0.5	1.7	(-2.4, 5.8)
6	1.1	-1.5	2.7	(-1.6, 6.9)
8	-0.3	1.6	-1.9	(-5.5, 1.8)
10	-0.5	-0.5	-0.1	(-3.8, 3.6)
12	1.3	-1.5	2.8	(-1.4, 7.0)
14	-0.8	-3.5	2.7	(-1.4, 6.8)
16	-2.9	-4.7	1.8	(-2.8, 6.3)
18	-0.9	-1.4	0.5	(-3.8, 4.8)
23.5	-1.3	-6.4	5.1	(1.3, 8.8)

5.2.1.2 Assay Sensitivity Analysis for Retigabine

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 6. The largest 90% lower confidence interval is 7.1 ms at 1 hour after dose with Bonferroni multiple endpoint adjustment of four time points. This indicates that an at least 5 ms $QTcF$ effect due to moxifloxacin can be detected from the study.

Table 6: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Moxifloxacin 400 mg

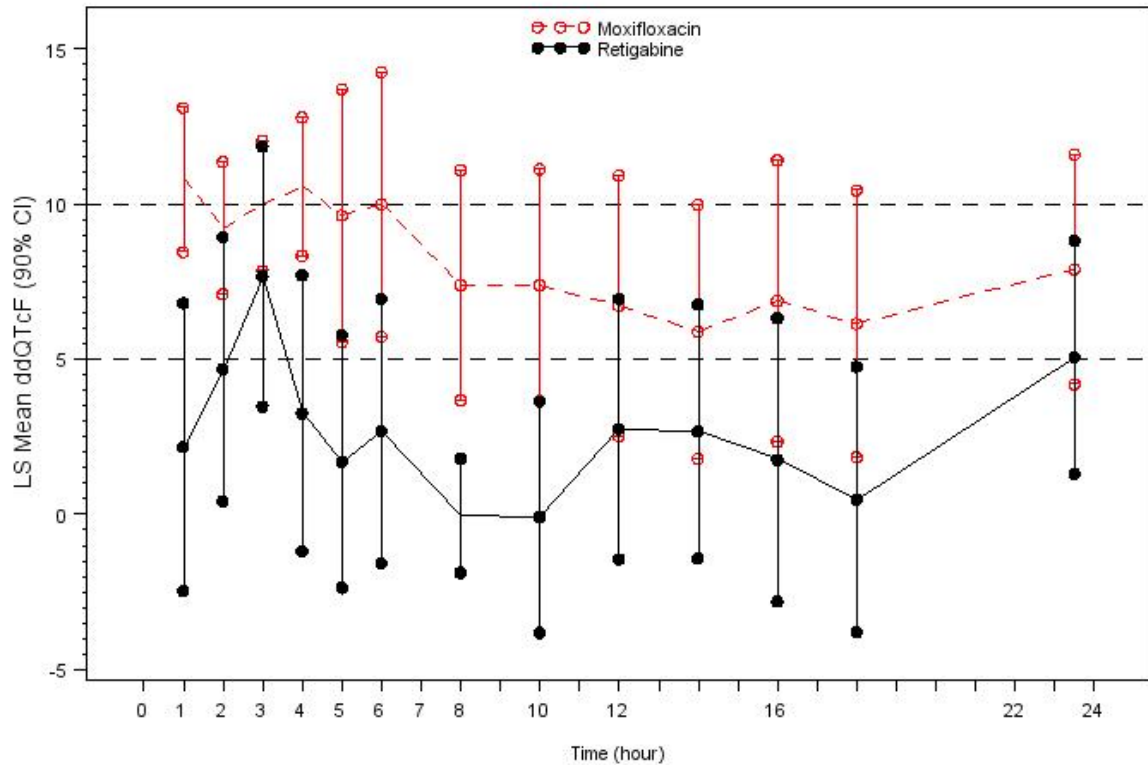
	Moxifloxacin	Placebo	$\Delta\Delta$ QTcF	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
1	8.3	-4.8	13.1	(7.1, 19.1)
2	9.8	-1.6	11.4	(5.8, 16.9)
3	10.2	-1.9	12.1	(6.6, 17.5)
4	10.2	-2.6	12.8	(7.0, 18.6)
5	9.2	-0.5	9.6	(4.3, 14.9)
6	8.4	-1.5	10.0	(4.5, 15.5)
8	9.0	1.6	7.4	(2.6, 12.2)
10	6.9	-0.5	7.4	(2.5, 12.2)
12	5.3	-1.5	6.7	(1.3, 12.2)
14	2.4	-3.5	5.9	(0.6, 11.2)
16	2.2	-4.7	6.9	(1.0, 12.8)
18	4.8	-1.4	6.1	(0.5, 11.7)
23.5	1.5	-6.4	7.9	(3.1, 12.7)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

5.2.1.3 Graph of $\Delta\Delta\text{QTcF}$ Over Time

The following figure displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups

Figure 4: Mean and 90% CI $\Delta\Delta\text{QTcF}$ Timecourse
DAY=22



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

No subject's QTcF was above 480 ms. Table 8 lists the categorical analysis results for ΔQTcF . No subject's change from baseline was above 60 ms.

Table 8: Categorical Analysis of $\Delta QTcF$

	Total N		Value$\leq$30		30<Value$\leq$60	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin	38	491	36 (94.7%)	487 (99.2%)	2 (5.3%)	4 (0.8%)
Placebo	39	507	39 (100%)	507 (100%)	0 (0.0%)	0 (0.0%)
Retigabine	38	490	36 (94.7%)	486 (99.2%)	2 (5.3%)	4 (0.8%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 9. The largest upper bound of the 2-sided 90% CI for the mean PR difference between retigabine group and placebo were 5.6 ms at 2 hours after dose.

The outlier analysis results for PR are presented in Table 11 and Table 12.

Table 9: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Groups of Retigabine

	Retigabine	Placebo	$\Delta\Delta$ PR	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
1	4.0	4.8	-0.8	(-5.4, 3.9)
2	4.8	3.6	1.2	(-3.1, 5.6)
3	4.3	5.8	-1.5	(-5.6, 2.6)
4	5.3	5.4	-0.1	(-4.4, 4.1)
5	3.4	3.5	-0.1	(-4.7, 4.4)
6	4.2	4.6	-0.3	(-4.5, 3.8)
8	6.1	4.9	1.2	(-2.8, 5.3)
10	4.2	5.1	-0.9	(-4.4, 2.6)
12	2.8	4.1	-1.3	(-5.4, 2.8)
14	2.0	2.1	-0.1	(-3.9, 3.8)
16	2.9	3.6	-0.7	(-4.6, 3.2)
18	0.5	4.4	-3.9	(-7.9, 0.2)
23.5	3.1	3.2	-0.1	(-3.9, 3.7)

Table 11: Categorical Analysis for PR

	T		Value $\leq$ 200		Value $>$ 200	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin	38	491	37 (97.4%)	478 (97.4%)	1 (2.6%)	13 (2.6%)
Placebo	39	507	34 (87.2%)	482 (95.1%)	5 (12.8%)	25 (4.9%)
Retigabine	38	491	34 (89.5%)	484 (98.6%)	4 (10.5%)	7 (1.4%)

Table 12: Categorical Analysis for Observations PR >200 ms under Treatment

Treatment Group	ID	1 hr	2 hr	10 hr	12 hr	16 hr	18 hr
Retigabine	014				212		
Baseline	014				189		
Retigabine	026			200		201	
Baseline	026			195		186	
Retigabine	107	205	204			201	207
Baseline	107	186	184			191	198
Retigabine	110				205		
Baseline	110				174		

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 13. The largest upper bound of the 2-sided 90% CI for the mean QRS change difference between retigabine and placebo were 1.3 ms at 12 hour after dose.

There is no subject who experienced QRS interval greater than 120 ms in any treatment arm.

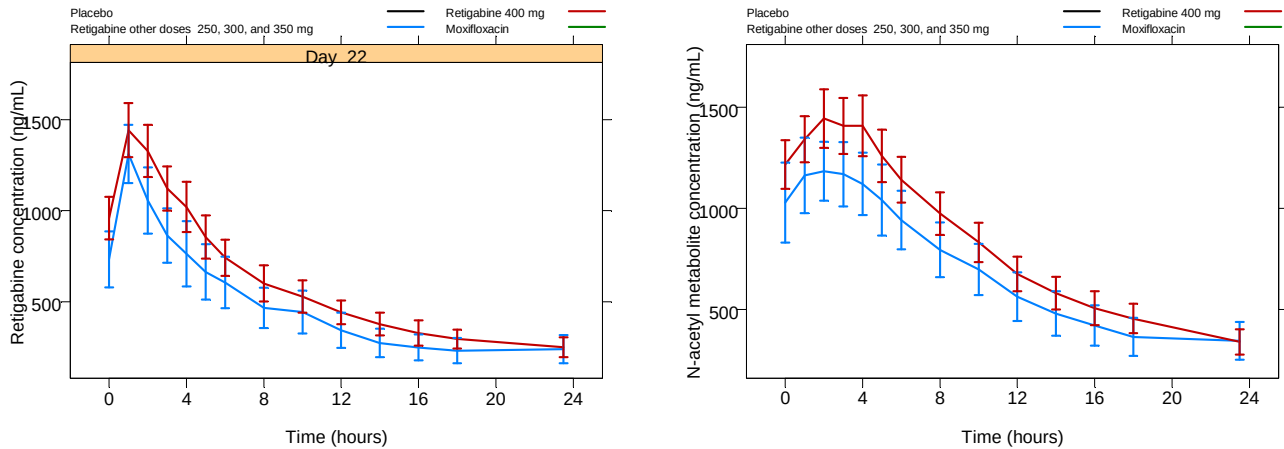
Table 13: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Groups of Retigabine

	Retigabine	Placebo	$\Delta\Delta$ QRS	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
1	0.1	1.6	-1.5	(-3.5, 0.5)
2	0.4	1.5	-1.0	(-3.1, 1.1)
3	0.5	1.6	-1.1	(-3.1, 0.9)
4	0.3	1.3	-1.0	(-3.0, 0.9)
5	0.1	0.9	-0.8	(-2.7, 1.1)
6	0.0	1.1	-1.1	(-2.8, 0.6)
8	0.2	1.3	-1.1	(-3.0, 0.8)
10	0.3	1.2	-0.9	(-2.5, 0.7)
12	0.5	1.0	-0.5	(-2.3, 1.3)
14	-0.0	1.0	-1.0	(-2.9, 0.8)
16	-0.7	0.9	-1.6	(-3.4, 0.1)
18	-0.4	0.6	-1.0	(-2.7, 0.8)
23.5	0.5	1.4	-0.9	(-2.6, 0.9)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

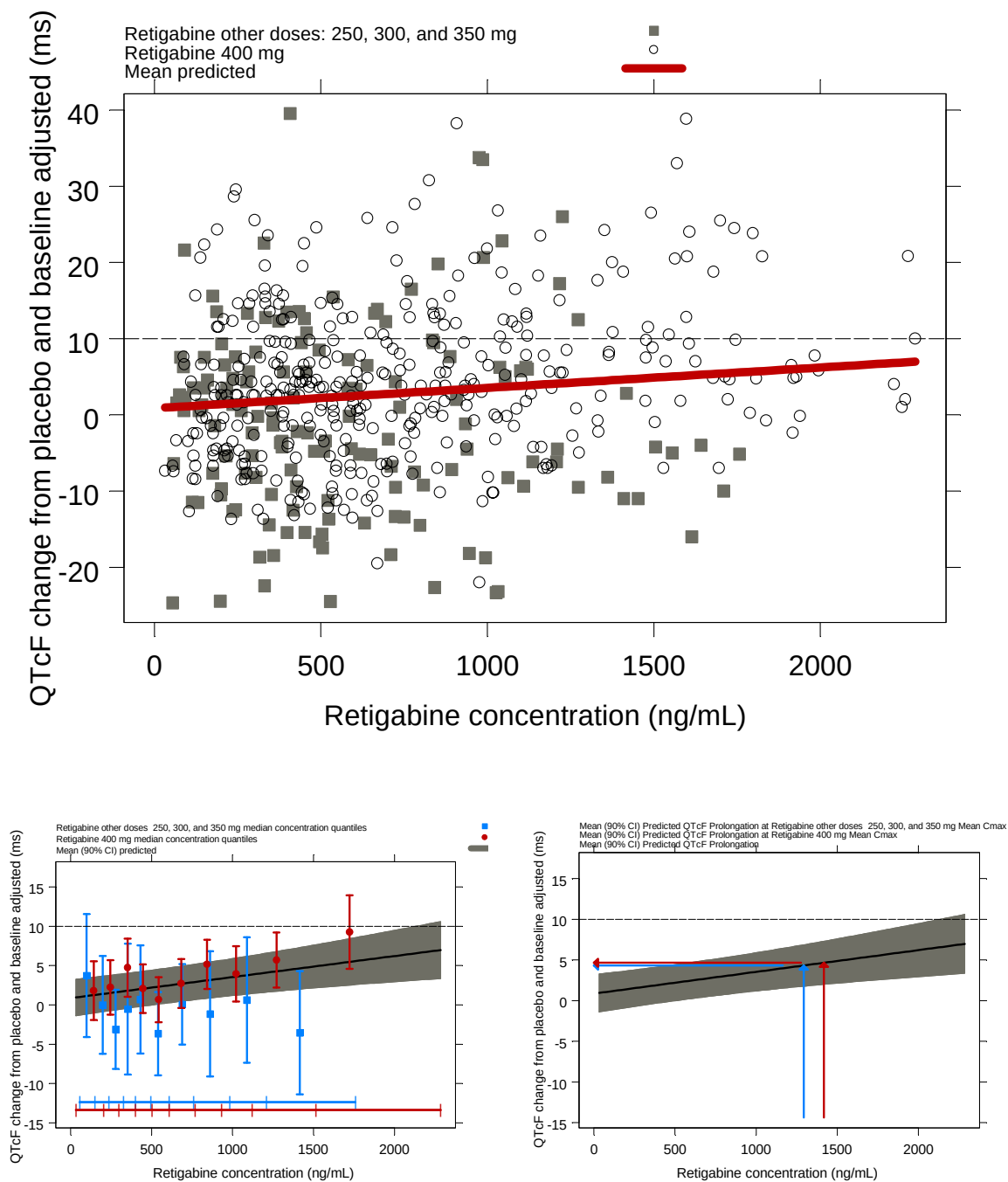
The 11 subjects who did not reach the highest final dose of 1200 mg/day (750 mg/day (5 subjects), 900 mg/day (4 subjects), and 1050 mg/day (2 subjects)) are grouped together into the sub-dose treatment. The mean concentration-time profiles of retigabine and its N-acetyl metabolite with the target dose (400 mg) and the sub-dose groups are illustrated in Figure 4.

Figure 4. Mean Concentration-time Courses of Retigabine (Left) and its N-acetyl Metabolite (Right) with the Highest Dose (Red Line) and the Sub-dose (Blue Line)



The relationship between $\Delta\Delta\text{QTcF}$ and retigabine concentrations is visualized in Figure 5. The slope of the exposure-response relationship is slightly but significantly greater than 0 (slope: 0.00227 with p-value: 0.0081). The upper 90% confidence boundary of the median concentration for the 10th-quantiles of the 1200 mg/day dose exceeds the clinical threshold per ICH E-14, 10 ms. Also in the quantile plot, the $\Delta\Delta\text{QTcF}$ in the 1200-mg/day dose group is consistently higher than in the sub-dose group. Therefore, the potential effect of retigabine on QT prolongation exists. However, the upper 90% confidence boundary of the median concentration for the 10th-quantiles for the 1200-mg/day dose is below 15 ms and the mean values of C_{max} for both the highest tolerated dose and sub-dose are all below 5 ms. Hence, the potential effect of retigabine on QT prolongation is likely to be small and should not have important clinical significance except perhaps in those subjects who are at the highest risk.

Figure 5. $\Delta\Delta$ QTcF vs. retigabine concentration. Observed data (Top), Concentration Quantile plot (Bottom Left), and Predicted $\Delta\Delta$ QTcF at mean C_{max} (Bottom Right).



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety Assessments

Three of the events identified to be of clinical importance per the ICH E14 guidelines, i.e. sudden cardiac death, syncope and seizure, did not occur in this study. There was one case each of syncope in the RTG and placebo groups reported as vasovagal.

5.4.2 ECG Acquisition and Interpretation

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics, over 97% of the ECGs were annotated in the primary lead (II) with V5 being the usual back-up lead. Less than 0.1% of ECGs were reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interpretation

There were no clinically relevant effects on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	200 mg TID, 300mg TID, 400 mg TID	
Maximum tolerated dose	400 mg TID in epileptic patients, although few patients received daily doses between 1600 mg and 2400 mg that were not well tolerated. In healthy volunteers, without titration, single oral dose of 400 mg were administered in several studies and were associated with AE (mainly CNS). Single oral doses greater than 600mg were associated with increased incidence of AEs.	
Principal adverse events	Dizziness, somnolence, confusion, speech disorders, vertigo, tremor, abnormal thinking, amnesia, paresthesia and diplopia	
Maximum dose tested	Single Dose	900 mg
	Multiple Dose	400 mg TID
Exposures Achieved at Maximum Tested Dose	Single Dose	1096 ng/mL (40%) for C_{max} 11915 ng·h/mL (22%) for AUC(0-t)
	Multiple Dose	<u>Healthy Subjects in Thorough QT study</u> 1501 ng/mL (32%) for C_{max} 7993 ng·h/mL (37%) for AUC(0-8) <u>Epileptic Subjects in Phase III Study 301</u> 1510 ng/mL (32%) for C_{max} 10100 ng·h/mL (35%) for AUC(0-8)
Range of linear PK	25 mg to 600 mg after single oral dose 200 to 400 mg TID	
Accumulation at steady state	Accumulation not determined for TID dosing regimen 100 mg q12h : 1.42 (40%) for C_{max} and 1.05 (22%) for AUC(τ) 200 mg q12h : 1.42 (33%) for C_{max} and 1.20 (19%) for AUC(τ) 250 mg q12h : 1.21 (19%) for C_{max} and 0.99 (18%) for AUC(τ)	
Metabolites	N-acetyl Retigabine: 1/3 to 1/5 activity in rodent models of electroshock protection and less than 1/10 activity in rodent models of partial seizure protection Retigabine N1-glucuronide: No activity Retigabine N1-glucuronide: No activity N-acetyl Retigabine N1-glucuronide: No activity N-acetyl Retigabine N2-glucuronide: No activity M7 metabolite : No activity	
Absorption	Absolute/Relative Bioavailability Mean (%CV)	58.3% (19%)
	*T _{max} Median (range)	1.5 h (0.3 -12.1)

Distribution	V _{ss} after IV dose 50 mg mean	2.96 L/Kg (2.61-3.36)
	% bound	80%
Elimination	Route	Oral 84% of dose in urine 14% of dose in feces No other route known
	*Terminal t _{1/2} Median (Range)	7.5 h (2.8-21.6)
	CL after 50 mg IV dose median (range)	9.49 ml/min/kg (8.67-10.4)
Intrinsic Factors	Age	<u>Elderly Men versus Young Men</u> C _{max} 16% lower and AUC 37% higher in elderly men <u>Elderly Women versus Young Women</u> C _{max} 9% higher and AUC 50% higher in elderly women
	Sex	<u>Young Women versus Young Men</u> C _{max} 56% higher and AUC 20% higher in young women <u>Elderly Women versus Elderly Men</u> C _{max} 103% higher and AUC 31% higher in elderly women
	Race	From a meta-analysis of Phase I studies, retigabine clearance was 20% lower in black subjects than in Caucasian subjects
	Hepatic & Renal Impairment	<u>Renal Impairment:</u> Mild: C _{max} no change and AUC 31% higher Moderate: C _{max} 43% higher and AUC 139% higher Severe: C _{max} no change and AUC 109% higher ESRD: C _{max} halved and AUC 118% higher <u>Hepatic Impairment:</u> Mild: C _{max} 27% lower and AUC 9% lower Moderate: C _{max} 31% higher and AUC 52% higher Severe: C _{max} 27% higher and AUC 109% higher

Extrinsic Factors	Drug interactions	Population PK analysis of Phase III studies in patients already taking AEDs showed that co-administration of lamotrigine resulted in a 6.7% lower clearance of retigabine Co-administration of lamotrigine (25 mg /day) with retigabine (200 mg single) dose resulted in a 15% increase in retigabine AUC but no change in C_{max} The population pharmacokinetic analysis showed no effect of carbamazepine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, topiramate or valproate on pharmacokinetics of retigabine.
	Food Effects	Administration of a high fat meal had no effect on the AUC of retigabine. For C_{max}, there was no effect of food was observed for the capsule formulation administered as a 200mg single dose. For the initial tablet (200mg single dose) and market image tablet (400 mg single dose), C_{max} increased by 14% and 38%, respectively.
Expected High Clinical Exposure Scenario	The highest clinical dose is 1200mg day (400 mg TID) <i>Amongst the intrinsic and extrinsic factors analysed the more significant increase in C_{max} and AUC are anticipated to occur in patients with moderate to severe renal impairment and in severe hepatic impairment.</i>	
*Median and range of T_{max} and t_{1/2} values was calculated from data obtained in biopharmaceutical studies 3065A1-100, 3065A1-106, 3065A1-110, VRX-RET-E22-104 and VRX-RET-E22-105		

6.2 STUDY ASSESSMENTS

Table 9-2 Schedule of Events

Study Phase	Screening	Baseline	Treatment Phase			Discharge ^a
	Day -21 through Day -2	Day -1	Day 1	Day 2 through Day 21	Day 22	Day 23
Informed consent	X					
Eligibility assessment	X					
Serology ^b	X					
Prior/concomitant medication assessment	X					
Urine screening for drugs of abuse	X	X				
Serum pregnancy test	X	X				
Randomization ^c		X				
Study drug administration ^d			X	X	X	
Pharmacokinetic blood samples ^e		X	X		X	X ^g
Blood samples for genotyping ^f		X				
Medical history	X	X				X ^g
Physical examination	X	X				X ^g
Safety digital electrocardiograms	X	X	X ^h	X ^{h,i}		
Vital signs	X	X	X	X	X	X ^g
12-lead ECG from H-12 ^j		X			X	X ^g
Safety laboratory (serum chemistry, hematology, urinalysis)	X	X				X ^g
Adverse event assessment	X	X	X	X	X	X ^g

^a Subjects were discharged 24 hours after the last dose.

^b Serology included tests for human immunodeficiency virus, hepatitis B surface antigen, and hepatitis C virus.

^c Randomization may have been performed at the end of Day -1 or on Day 1 immediately before dosing.

^d Subjects assigned to the retigabine group received 100 mg of retigabine 3 times a day on Days 1 through 3, followed by a retigabine dose that had been increased by 50 mg every 72 hours from Day 4 through Day 21, and a single 400-mg dose of retigabine on the morning of Day 22. Subjects assigned to the placebo group received placebo tablets 3 times a day on Days 1 through 21, and a single dose of placebo on the morning of Day 22. Subjects assigned to the moxifloxacin group received placebo on Days 1 through 21, and a single 400-mg moxifloxacin tablet on the morning of Day 22.

^e To minimize the effect of phlebotomy on the comparisons of QT measurement, blood samples were collected at baseline from all subjects at times matching the pharmacokinetic blood sampling on Day 22. No analysis was performed on the blood samples taken at baseline. Blood samples were also obtained before dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dosing. On Day 22, plasma samples for both retigabine and the N-acetyl metabolite of retigabine were obtained from all subjects on all treatments to maintain comparable study conditions and the blind, but were only analyzed for the active treatment groups.

^f Blood was obtained from all subjects to determine UDP-glucuronosyltransferase and N-acetyl transferase genotypes.

^g Or at the time of early discontinuation.

^h Collected on-site at 2 to 3 hours after the morning dose.

ⁱ On Days 3, 6, 9, 12, 15, 18, and 21.

^j Flash card was placed in the morning of Days -1 and 22. Five ECGs within 5 minutes were obtained before dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dosing on Days -1 and 22.

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

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

/s/

HAO ZHU
01/29/2010

JIANG LIU
01/29/2010

QIANYU DANG
01/29/2010

JOANNE ZHANG
01/29/2010

SUCHITRA M BALAKRISHNAN
01/29/2010

NORMAN L STOCKBRIDGE
01/29/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022345 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Potiga Established/Proper Name: retigabine Dosage Form: tablets Strengths: 50 mg, (b) (4) 200 mg, 300 mg, 400 mg		
Applicant: Valeant Pharmaceuticals North America Agent for Applicant (if applicable):		
Date of Application: October 30, 2009 Date of Receipt: October 30, 2009 Date clock started after UN:		
PDUFA Goal Date: August 30, 2010	Action Goal Date (if different):	
Filing Date: December 29, 2009	Date of Filing Meeting: December 15, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Adjunctive therapy in refractory epilepsy patients with partial-onset seizures.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 53,950				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes , explain in comment column.				
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application:			
	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:			
	☒ Not in arrears ☐ In arrears			
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?			X	
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X	
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?			X	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)	X			
If yes, # years requested: 5				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?		X		Confirmed with Martha Heimann, Ph.D.
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? If yes , date consult sent to the Controlled Substance Staff: November 13, 2009	X			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (Certification is not required for supplements if submitted in the original application)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	X			

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			Ask Ginneh about PPSR @ Filing mtg. Sent email on 11/20/09.
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	X			Confirmed with Ginneh Stowe. Sent email on 11/20/09.
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Sent 1/19/10.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Sent 12/4/09.
REMS consulted to OSE/DRISK?	X			Sent 12/4/09.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			Sent 11/20/09.
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			
<i>If yes, specify consult(s) and date(s) sent:</i> QT-IRT (11/12/09) Carcinogenicity/Statistics (11/12/09) Statistics (11/12/09) CSS (11/13/09) DMEPA/OSE (11/20/09) DRISK/OSE (12/4/09) DSI (1/4/10) DDMAC (1/19/10)				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): EOP2/CMC (10/25/04) EOP2 (12/8/04)	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): preNDA comments (10/11/07) pre NDA follow-up to comments (8/31/09)	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): December 16, 2002 June 3, 2004 June 29, 2005 August 18, 2005	X			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 15, 2009

BLA/NDA/Supp #: 022345

PROPRIETARY NAME: Potiga

ESTABLISHED/PROPER NAME: Retigabine

DOSAGE FORM/STRENGTH: Tablets 50 mg, (b) (4) 200 mg, 300 mg, 400 mg

APPLICANT: Valeant Pharmaceuticals North America

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Adjunctive therapy in refractory epilepsy patients with partial-onset seizures.

BACKGROUND: Retigabine is a first in class neuronal potassium channel opener for the treatment of partial-onset seizures. The international clinical program described in this NDA is comprised of 44 studies, including 28 Phase I studies, five completed Phase II studies; two completed Phase III studies; and six long-term, open-label extension studies (of which, extensions of two Phase III studies remain ongoing). In addition, there is an ongoing compassionate use program for a limited number of patients with refractory partial seizures and there have been two Phase II studies conducted to support other potential indications.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stephanie N. Keefe	Y
	CPMS/TL:	Jacqueline H. Ware	Y
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		Y
Clinical	Reviewer:	Steven Dinsmore	Y
	TL:	Norman Hershkowitz	Y
Clinical Pharmacology	Reviewer:	Ta-Chen Wu	Y
	TL:	Angela Men	Y

Biostatistics	Reviewer:	Ohidul Siddiqui	N
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ed Fisher	Y
	TL:	Lois Freed	N
Statistics (carcinogenicity)	Reviewer:	Atiar Mohammed Rahman	Y
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	Mohan Sapru Martha Heimann	Y Y
	TL:	Ramesh Sood Angelica Dorantes	N N
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kellie Taylor	N
	TL:	Tara Turner	Y
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	N
	Reviewer:	Barbara Fuller	N
Bioresearch Monitoring (DSI)	Reviewer:	Tony El Hage	N
	TL:	Tejashri Purohit-Sheth	N

ONDQA Biopharmaceuticals Reviewer	John Duan	N
Pharmacometrics	Yaning Wang	Y
	Joo-Yeon Lee	Y
Pharmacogenomics	Issam Zineh	N
	Li Zhang	Y
Compliance (OC/DMPQ)	Francis Godwin	Y
	Jaewon Hong	N
PEDS	Virginia Elgin/Hari Sachs	Y/Y
	Ginneh Stowe	Y
	(OCP) Allen Rudman, Lily Mulugeta	N, Y
	and Dionna Green	N
CSS	Katherine Bonson	Y
	Silvia Calderon	N
	Michael Klein	N
Urology	Mark Hirsch	N
	Chong Kim	N

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? If yes, list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? If no, explain:	☐ YES ☐ NO
• Electronic Submission comments List comments:	☐ Not Applicable
CLINICAL Comments: Safety issues – urologic signal and cardiac signal. Lots of foreign sites; 3 pivotal trials. Financial disclosure required for pivotal studies. Triggers MedGuide only REMS; possible REMS memo from Norm (Kelly to advise on letter and Memo).	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? Comments: (1/15/10) Dr. Temple to discuss with John Jenkins. If no, for an original NME or BLA application, include the reason. For example: ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☐ NO ☒ To be determined Reason:

If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
PEDS Comments: Waiver for 0-1month is likely appropriate as there are too few patients. Deferral for 1month- 16y.o. --- safety issue; formulation issue. --Need protocol submit dates, initiation dates/completion, report submission dates. -- Need to further discuss PPSR. (Is it a Pediatric plan or PPSR?)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments: Has traditional PK/population PK/meta-analysis for genomics evaluation. Well over 50 studies. Issue: some reports are image files, which need to be converted to alpha numeric files. An annotated WORD version of the labeling is being requested.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments: Fileable; working on response to sponsor's 12/4/09 submission (response to Stat IR).	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: Gen-tox issue is likely to be conveyed in 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
COMPLIANCE	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments: Will inspect Drug product manufacturer and drug substance manufacturer. Mutagenicity issue with drug substance. ONDQA will participate.	☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: Issues for 74-day letter: sponsor has made manufacturing changes that require further data. Polymorph issues. Stability issues.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>DRISK</u> Comments: MedGuide only REMS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments: Compliance to inspect drug product and drug substance.	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>DMEPA</u> Comments: Tradename due on 2/19/10. Established name is problematic.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CSS</u> Comments: 344 page liability; 9% euphoria.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
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REGULATORY PROJECT MANAGEMENT

Signatory Authority: Bob Temple

21st Century Review Milestones (see attached) (optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES
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☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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

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

/s/

STEPHANIE N KEEFE
01/28/2010