CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022345Orig1s000

REMS

APPENDIX A – REMS

Initial REMS Approval: 06/2011

NDA 22-345 POTIGA™ (ezogabine) Tablets

Drug Class: Anticonvulsant

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

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

II. REMS ELEMENTS

A. Communication Plan

For Healthcare Professionals

Valeant Pharmaceuticals North America will implement a communication plan to support the implementation of this REMS that includes the following elements:

1. A Dear Healthcare Professional (HCP) Letter designed to disseminate information about the risk of urinary retention with POTIGA. Within the first four weeks of retail availability of POTIGA, and annually for the next two years, the Dear Healthcare Professional (HCP) letters will be mailed to the following audiences:

    a. Prescribing physicians (i.e., Epileptologists, Neurologists and Neurosurgeons) and physicians who may evaluate and treat patients with possible urinary retention (i.e., Urologists and Emergency Room Physicians)

    b. Pharmacists dispensing POTIGA tablets and the Medication Guide

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

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

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

The following materials are part of the REMS and are attached:

- Dear Healthcare Professional Letter (**Attachment A**)
- Dear Pharmacist Letter (**Attachment B**)
- REMS Program website for healthcare professionals (**Attachment C**)

B. Timetable for Submission of Assessments

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

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment.

The Sponsor will submit each assessment so it will be received by the FDA on or before the due date.

ATTACHMENT A – Dear Healthcare Professional Letter – Physicians

IMPORTANT DRUG WARNING

Subject: Risk of Urinary Retention with POTIGA

Dear Healthcare Professional

The purpose of this letter is to inform you of important safety information for POTIGA™ (ezogabine) Tablets, approved by the Food and Drug Administration (FDA) for adjunctive treatment of partial onset seizures in patients 18 years of age and older. As a potassium channel opener, POTIGA can reduce the contractility of urinary bladder smooth muscle which can cause urinary retention.

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for POTIGA to ensure the benefits of the drug outweigh the risk of urinary retention and its associated morbidities. As one element of the REMS, we are providing this letter to further communicate this risk.

Risk of Urinary Retention

POTIGA caused urinary retention in clinical trials. Urinary retention was reported in 29 of 1365 (approximately 2%) patients receiving POTIGA in open-label and placebo controlled epilepsy trials with 4 (14%) of these patients requiring catheterization for urinary retention. Following discontinuation of POTIGA, all 4 patients who required catheterization for urinary retention were able to void spontaneously; however, 1 of the 4 patients also required continued intermittent self-catheterization following discontinuation of POTIGA. Hydronephrosis occurred in 2 patients, one of whom had associated renal function impairment that resolved upon discontinuation of POTIGA. Hydronephrosis was not reported in placebo patients. An assessment of a patient's risk of urinary retention, including medical history and concomitant medication use, should be made for all patients before initiating treatment with POTIGA.

The Prescribing Information for POTIGA states in the *Warnings and Precautions* section that because of the increased risk of urinary retention on POTIGA, urologic symptoms should be carefully monitored. Closer monitoring is recommended for patients who have other risk factors for urinary retention (e.g., benign prostatic hyperplasia [BPH]), patients who are unable to communicate clinical symptoms (e.g., cognitively impaired patients), or patients who use concomitant medications that may affect voiding (e.g., anticholinergics). In these patients, a comprehensive evaluation of urologic symptoms prior to and during treatment with POTIGA may be appropriate.

Prescribers should inform all patients that:

- POTIGA may cause urinary retention, including urinary hesitation and dysuria
- Patients should seek immediate medical attention if they experience any symptoms of urinary retention, are unable to urinate and/or have urinary pain

Urologists and Emergency Room Physicians may be asked to evaluate patients with respect to suitability for treatment with POTIGA or to evaluate and/or treat patients with potential urinary retention.

Medication Guide

A Medication Guide is available for POTIGA and contains important safety information for patients. Specifically, the Medication Guide includes information on symptoms of urinary retention described as being unable to start urinating, having trouble emptying the bladder, having a weak urine stream, or having pain with urination. The Medication Guide instructs patients to call their healthcare provider right away if they experience any of these symptoms.

Additional copies of the Medication Guide for POTIGA are available from:

- the toll-free medical information line at 1-888-825-5249
- an informational website for POTIGA: www.potiga.com

Reporting Adverse Events

If you become aware of an adverse event involving POTIGA please contact:

- GlaxoSmithKline at 1-800-334-4153 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

This letter is not a comprehensive description of the risks with the use of POTIGA. Please read the accompanying full Prescribing Information and Medication Guide for a complete description of these risks.

ATTACHMENT B – Dear Healthcare Professional Letter – Pharmacist

IMPORTANT DRUG WARNING

Subject: Risk of Urinary Retention with POTIGA

Dear Pharmacist

The purpose of this letter is to inform you of important safety information for POTIGA™ (ezogabine) Tablets, approved by the Food and Drug Administration (FDA) for adjunctive treatment of partial onset seizures in patients 18 years of age and older. As a potassium channel opener, POTIGA can reduce the contractility of urinary bladder smooth muscle which can cause urinary retention.

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for POTIGA to ensure the benefits of the drug outweigh the risk of urinary retention and its associated morbidities.

As one element of the REMS, we are providing this letter to further communicate these risks.

Risk of Urinary Retention

POTIGA caused urinary retention in clinical trials. The Prescribing Information for POTIGA states in the *Warnings and Precautions* section that because of the increased risk of urinary retention on POTIGA, urologic symptoms should be carefully monitored. Closer monitoring is recommended for patients who have other risk factors for urinary retention (e.g., benign prostatic hyperplasia [BPH]), patients who are unable to communicate clinical symptoms (e.g., cognitively impaired patients), or patients who use concomitant medications that may affect voiding (e.g., anticholinergics).

Patients should be informed that POTIGA may cause urinary retention (including urinary hesitation and dysuria). If patients experience any symptoms of urinary retention, inability to urinate, and/or pain with urination, they should be instructed to seek immediate medical assistance, as these symptoms may indicate possible acute urinary retention.

As a Pharmacist, you have a key role in communicating these risks by providing the Medication Guide with every prescription filled for POTIGA and counselling patients as appropriate.

Medication Guide

A Medication Guide is available for POTIGA and contains important safety information for patients. Specifically, the Medication Guide includes information on symptoms of urinary retention described as being unable to start urinating, having

trouble emptying the bladder, having a weak urine stream, or having pain with urination. The Medication Guide instructs patients to call their healthcare provider right away if they experience any of these symptoms. .

The Medication Guide will be attached to every bottle and enclosed in each sample pack of POTIGA. The label of each container or package of POTIGA will include a prominent instruction to dispensers to provide a Medication Guide, which is attached to the package. The instruction states "*Dispense the accompanying Medication Guide to each patient*."

Additional copies of the Medication Guide for POTIGA are available from:

- the toll-free medical information line at 1-888-825-5249
- an informational website for POTIGA: www.potiga.com

Reporting Adverse Events

If you become aware of an adverse event involving POTIGA please contact:

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Patients and Caregivers
Click Here

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

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

Please review the following Dear Healthcare Professional Letters:

- **Prescribing Physicians**
- **Pharmacists**

Please consult complete **Prescribing Information** including the **Medication Guide** for POTIGA.

INDICATIONS AND USAGE

POTIGA is a potassium channel opener indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older.

IMPORTANT SAFETY INFORMATION FOR POTIGA

WARNINGS AND PRECAUTIONS

Urinary Retention

POTIGA can cause urinary retention. In clinical trials, urinary retention was generally reported within the first 6 months of treatment, but was also observed later. Patients should be carefully monitored for urologic symptoms, because of the increased risk of urinary retention while taking POTIGA. Closer monitoring is recommended for patients who have other risk factors for urinary retention (e.g., benign prostatic hyperplasia [BPH]), are unable to communicate clinical symptoms (e.g., cognitively impaired patients), or use concomitant medications that may affect voiding (e.g., anticholinergics). In these patients, a comprehensive evaluation of urologic symptoms prior to and during treatment with POTIGA may be appropriate.

Neuro-Psychiatric Symptoms

Confusional state, psychotic symptoms, and hallucinations were reported more frequently as adverse reactions in patients treated with POTIGA than in those treated with placebo in epilepsy trials. Discontinuations resulting from these reactions were more common in the group treated with POTIGA. Effects were dose-related and generally appeared within the first 8 weeks of treatment. Half of the patients in the controlled trials who discontinued POTIGA due to hallucinations or psychosis required hospitalization. Approximately two thirds of patients with psychosis in controlled trials had no prior psychiatric history. The psychiatric symptoms in the vast majority of patients in both controlled and open-label trials resolved within 7 days of discontinuation of POTIGA. Rapid titration at greater than recommended doses appeared to increase the risk of psychosis and hallucinations.

Dizziness and Somnolence

POTIGA causes dose-related increases in dizziness and somnolence. In clinical trials these adverse reactions occurred most often during the titration phase. For those patients who continued on POTIGA, these adverse reactions appeared to diminish with continued use.

QT Interval Effect

A study of cardiac conduction showed that POTIGA produced a mean 7.7-msec QT prolongation in healthy volunteers titrated to 400 mg 3 times daily. The QT-prolonging effect occurred within 3 hours. The QT interval should be monitored when POTIGA is prescribed with medicines known to increase QT interval and in patients with known prolonged QT interval, congestive heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia.

Suicidal Thoughts or Behavior

- Antiepileptic drugs (AEDs), including POTIGA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication.
- Patients treated with any antiepileptic drug for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
- Anyone considering prescribing POTIGA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
- Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts or behavior or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Withdrawal Seizures

As with all AEDs, when POTIGA is discontinued, it should be withdrawn gradually when possible to minimize the potential of increased seizure frequency. The dosage of POTIGA should be reduced over a period of at least 3 weeks, unless safety concerns require abrupt withdrawal.

ADVERSE REACTIONS

Adverse Reactions Leading to Discontinuation

In 3 controlled clinical studies, 25% of patients receiving POTIGA (199/813) and 11% of patients receiving placebo (45/427) discontinued treatment because of treatment-emergent adverse reactions. The most common adverse reactions leading to withdrawal in patients receiving POTIGA were dizziness (6%), confusional state (4%), fatigue (3%), and somnolence (3%).

Most Common Adverse Reactions

The most frequently reported adverse reactions in patients receiving POTIGA vs placebo (≥4% and occurring approximately twice the placebo rate) were dizziness (23% vs 9%), somnolence (22% vs 12%), fatigue (15% vs 6%), confusional state (9% vs 3%), vertigo (8% vs 2%), tremor (8% vs 3%), abnormal coordination (7% vs 3%), diplopia (7% vs 2%), disturbance in attention (6% vs <1%), memory impairment (6% vs 3%), asthenia (5% vs 2%), blurred vision (5% vs 2%), gait disturbance (4% vs 1%), aphasia (4% vs <1%), dysarthria (4% vs <1%), and balance disorder (4% vs <1%). In most cases the reactions were of mild or moderate intensity.

DRUG INTERACTIONS

- Ezogabine plasma levels may be reduced by concomitant administration of phenytoin or carbamazepine. Consider an increase in the dosage of POTIGA when adding phenytoin or carbamazepine.
- Administration of POTIGA at therapeutic doses may increase digoxin serum concentrations. Serum levels of digoxin should be monitored.

OTHER INTERACTIONS

- Alcohol increased systemic exposure to POTIGA. Patients should be advised of possible worsening of ezogabine's general dose-related adverse reactions if they take POTIGA with alcohol.
- Ezogabine has been shown to interfere with clinical laboratory assays of both serum and urine bilirubin, which can result in falsely elevated readings.

USE IN SPECIFIC POPULATIONS

- Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Based on animal data, POTIGA may cause fetal harm. POTIGA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- It is not known whether POTIGA is excreted in human milk. However, POTIGA and/or its metabolites are present in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from POTIGA, a decision should be made as to whether to breastfeed or discontinue the drug, taking into account the importance of the drug to the mother.
- The safety and effectiveness of POTIGA in patients under 18 years of age have not been established.

DRUG ABUSE AND DEPENDENCE

POTIGA can be abused or lead to drug dependence. There are no adequate data to assess the ability of POTIGA to induce symptoms of withdrawal indicative of physical dependence. However, the ability of POTIGA to produce psychological dependence is suggested by adverse event reports of euphoric mood and euphoria.

IMPORTANT DOSING CONSIDERATIONS

- The dosage should be increased gradually at weekly intervals by no more than 50 mg 3 times daily (no more than 150 mg per day) up to a maintenance dosage of 200 to 400 mg 3 times daily (600 to 1,200 mg per day), based on individual response and tolerability.
- In the controlled clinical trials, 400 mg 3 times daily showed limited evidence of additional improvement in seizure reduction, but an increase in adverse events and discontinuations, compared to the 300 mg 3 times daily dosage.
- Dosing adjustments are required in:
  - Patients 65 years of age and older
  - Patients with creatinine clearance <50 mL/min or patients with end-stage renal disease (ESRD) receiving dialysis treatments
  - Patients with moderate or severe hepatic impairment

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

/s/

ELLIS F UNGER
06/10/2011