APPENDIX A – REMS

Initial REMS Approval: 06/10/2011
Most Recent Modification: 03/2012

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

GlaxoSmithKline LLC (GSK) 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 from that date 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. There are two ways that Healthcare Professionals (HCPs) can access the REMS Program information for POTIGA on the internet. The REMS Program website for HCPs will be accessed directly from the homepage for POTIGA (www.potiga.com) via the “for HCP” link. In addition, this page will automatically be shown when HCPs visit GSK’s professional website portal www.gsksource.com and click on product information 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 links to other product information for POTIGA.

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

GSK will submit assessments of the REMS to FDA 1, 2, 3, and 7 years from the date of initial approval of the REMS (June 10, 2011).

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.

GSK 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 5 (17%) of these patients requiring catheterization for urinary retention. POTIGA was discontinued in 4 patients who required catheterization. Following discontinuation, these 4 patients were able to void spontaneously; however, 1 of the 4 patients continued intermittent self-catheterization. A fifth patient continued treatment with POTIGA and was able to void spontaneously after catheter removal. 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](http://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](http://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.

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

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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:

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

/s/

RUSSELL G KATZ
03/19/2012