DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022345/S-006

SUPPLEMENT APPROVAL
REMS MODIFICATION NOTIFICATION

GlaxoSmithKline, LLC
Attention: Mark A. Baumgartner, R. Ph.
Senior Director, Global Regulatory Affairs
5 Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Baumgartner:

Please refer to your Supplemental New Drug Application (sNDA) dated December 13, 2012, received December 13, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for POTIGA (ezogabine) tablets 50 mg, 200 mg, 300 mg, 400 mg.

We acknowledge receipt of your amendments dated December 21, 2012; February 13, 2013; February 28, 2013; April 5, 2013; April 19, 2013; April 23, 2013; May 10, 2013; May 21, 2013; June 24, 2013; August 12, 2013; August 15, 2013; and August 22, 2013.

This "Prior Approval" supplemental new drug application provides for changes to the labeling for POTIGA (ezogabine) regarding the risks of pigmentary abnormalities of the retina, potential vision loss, and skin discoloration.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

Your approved Medication Guide will become part of the risk evaluation and mitigation strategy (REMS) in pending supplement NDA 022345/S-(b) (4), when approved.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

The REMS for POTIGA (ezogabine) was originally approved on June 10, 2011, and a REMS modification was approved on March 19, 2012. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for POTIGA (ezogabine) must be modified to ensure that the benefits of the drug outweigh its risks.

We acknowledge receipt of your REMS modification submission dated July 12, 2013. Your submission did not, however, contain all of the elements that we consider to be necessary to ensure that the benefits of the drug outweigh its risks, including the risks of pigmentary abnormalities of the retina, potential vision loss, and skin discoloration.

Your proposed REMS modification submission must include a Medication Guide, a revised communication plan, and Elements to Assure Safe Use to address the new safety information pertaining to the risks of retinal pigmentary abnormalities, potential vision loss, and skin discoloration. In sum, we are requiring that the following be included in the REMS:

> **Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Potiga poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Potiga. FDA has determined that Potiga is a product with risks of retinal pigmentary abnormalities, potential vision loss, skin discoloration, and urinary retention that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Potiga.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Potiga.

Communication Plan: We have determined that a revised communication plan targeted to healthcare providers who are likely to prescribe Potiga will support implementation of the elements of your REMS in the first month and annually for the first three years after the approval of the REMS modification. The communication plan must provide for the dissemination of information about the risks of retinal pigmentary abnormalities, potential vision loss, skin discoloration, and urinary retention.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a Communication Plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:

- Healthcare providers are specially certified or trained [section 505-1(f)(3)(A)]
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified [section 505-1(f)(3)(B)]
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions [section 505-1(f)(3)(D)]
- Each patient using the drug is subject to certain monitoring [section 505-1(f)(3)(E)]
- Each patient using the drug is enrolled in a registry [section 505-1(f)(3)(F)]

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Timetable for Submission of Assessments: The timetable for submission of assessments of the proposed, modified REMS must be revised to the following: GSK will submit assessments of the REMS to the FDA annually in years one, two, three, four, five, and seven from the date of initial approval of the Potiga 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 should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

The proposed REMS modification submission should include a new proposed REMS that shows the complete previously approved REMS with all proposed modifications highlighted and new and revised REMS materials.

In addition, the submission should include an update to the REMS supporting document that includes the rationale for and description of all proposed modifications and any impact the proposed modifications would have on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS with the elements described above is necessary to ensure that the benefits of Potiga outweigh the risks, you must submit an amendment to your proposed REMS modification submitted on July 12, 2013 within 30 days of the date of this letter. Specifically, the amendment to your July 12, 2013 proposed REMS modification must include the risk of skin discoloration as a risk to be mitigated by your REMS and the approved Medication Guide as an element of the REMS.

We will continue the review of your proposed modified REMS upon receipt of your amendment to your July 12, 2013 submission.

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

NDA 022345
PROPOSED REMS MODIFICATION-AMENDMENT

If you do not submit electronically, please send 5 copies of your submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any

new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Stephanie N. Parncutt, M.H.A., Regulatory Health Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

Alice Hughes, M.D.
Deputy Director of Safety
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ALICE HUGHES
09/06/2013