CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

201635Orig1s000

Trade Name: Trokendi XR

Generic Name: topiramate

Sponsor: Supernus Pharmaceuticals, Inc.

Approval Date: August 16, 2013

Indications:

- Initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut syndrome.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201635Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201635Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201635

NDA APPROVAL

Supernus Pharmaceuticals, Inc.
Attention: Tami T. Martin, RN, Esq.
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) dated January 13, 2011, received January 14, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trokendi XR (topiramate) extended-release capsules, 25 mg, 50 mg, 100 mg, and 200 mg.

We acknowledge receipt of your amendments dated June 10, 2013, June 17, 2013, June 20, 2013, and August 5, 2013. The June 17, 2013, amendment constituted a complete response (i.e., class 1 resubmission) to our June 7, 2013, action letter.

This new drug application provides for the use of Trokendi XR (topiramate) extended-release capsules for the following indications:

- initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures
- adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures
- adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut syndrome

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

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on June 17, 2013, and June 20, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 201635." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use as:

1. adjunctive therapy in patients 6 years to less than 17 years of age with partial onset or primary generalized tonic-clonic seizures
2. adjunctive therapy in patients 6 years to less than 17 years of age with seizures associated with Lennox-Gastaut syndrome
3. initial monotherapy in patients 10 years to less than 17 years of age with partial onset or primary generalized tonic-clonic seizures

Therefore, no additional studies are needed in these pediatric age groups for these indications.

We are waiving the pediatric study requirement for the following indications and age groups because studies are impossible or highly impracticable (because of the small number of patients and the difficulty diagnosing such age groups):

1. Adjunctive therapy in partial onset seizures (POS): Birth to less than 1 month old
2. Initial monotherapy in POS and primary generalized tonic-clonic (PGTC) seizures: Birth to less than 2 years old
3. Adjunctive therapy in primary generalized tonic-clonic seizures, and Adjunctive therapy in Lennox-Gastaut Syndrome (LGS): Birth to less than 2 years old

We are deferring submission of your pediatric studies for the following indications and age groups because this product is ready for approval for use in adults and the pediatric studies have not been completed**:**

1. Adjunctive therapy in partial onset seizures (POS): 1 month to less than 6 years old
2. Initial monotherapy in POS and primary generalized tonic-clonic (PGTC) seizures: 2 years to less than 10 years old
3. Adjunctive therapy in primary generalized tonic-clonic seizures, and Adjunctive therapy in Lennox-Gastaut Syndrome: 2 years to less than 6 years old

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2080-1 Develop an age appropriate formulation of Trokendi XR (topiramate) extended-release capsules that can be used in children 1 month to less than 6 years old.

Final Report Submission: August 31, 2015

2080-2 A study to evaluate the pharmacokinetics (PK) and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 2080-1, in children ages 2 years to less than 6 years with partial onset seizures (POS), primary generalized tonic-clonic (PGTC) seizures, and/or Lennox-Gastaut syndrome (LGS), and evaluating bioavailability after administration once daily relative to bioavailability of the reference listed drug, Topamax, given twice daily.

Final Protocol Submission: November 30, 2015
Study Completion: November 30, 2018
Final Report Submission: May 31, 2019

If similar bioavailability is not established for the age-appropriate formulation in PMR 2080-2, additional adjunctive therapy efficacy and safety studies for children ages 2 years to less than 6 years with POS, PGTC seizures, and LGS will be required.

2080-3 A study to evaluate the PK and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 2080-1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

Final Protocol Submission:	February 28, 2016
Study Completion:	February 28, 2019
Final Report Submission:	August 31, 2019

2080-4 An adequately controlled study to assess the efficacy and safety of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 2080-1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

Final Protocol Submission:	November 30, 2019
Study Completion:	November 30, 2024
Final Report Submission:	August 31, 2025

Submit the protocol(s) to your IND 101670, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

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

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA

2253. For instruction on completing the Form FDA 2253, see 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.

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 Taura Holmes, PharmD, Regulatory Project Manager, via telephone at (301) 796-1932 or via email at Taura.Holmes@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling (Package Insert and Medication Guide)

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

/s/

ERIC P BASTINGS
08/16/2013