CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201635Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	August 13, 2013
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	201635
Applicant	Supernus Pharmaceuticals
Date of Submission	June 17, 2013
PDUFA Goal Date	August 18, 2013
Proprietary Name / Established (USAN) names	Topiramate XR/ Trokendi XR
Dosage forms / Strength	Capsules 25, 50, 100, and 200 mg
Proposed Indication(s)	1. Partial Onset Seizures (monotherapy in patients ≥ 10 years and adjunctive treatment in patients ≥ 6 years) 2. Primary Generalized Tonic-Clonic Seizures (monotherapy in patients > 10 years and adjunctive treatment in patients > 6 years) 3. Seizures Associated with Lennox- Gastaut Syndrome (adjunctive treatment in patients > 6 years).
Recommended:	Approval

1. Introduction and Background

Trokendi XR is an extended release formulation of the referenced label drug Topamax (topiramate). Topamax is labeled for twice daily use whereas Trokendi is labeled for once a day. use. Topamax is presently approved for monotherapy and adjunctive therapy for seizures classified as partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in patients older 2 years and above as well as adjunctive treatment in patients with seizures associate with Lennox-Gastaut syndrome (LGS) in patients 2 years and above.

In the first supplement to this IND, the Sponsor requested approval for Trokendi's seizure indications, based upon a PK analysis where they demonstrated that not only did their product meet traditional bioequivalence standards, but it met bioequivalence standards based upon a more rigorous analysis. This analysis involved the comparison of Trokendi with the RLD at multiple concentration- time points and cumulative AUCs over a 24 hour. Using this more rigorous analysis, their product largely met bioequivalence using standard conventional statistical standards. The Division found the argument convincing and agreed that an approval should be awarded. However, because there was still patent protected information in the proprietary label regarding safety outcomes in 1 to 24 month old children, and that information could not be legally carved out, a tentative approval action was made. The exclusivity of this information would expire on June 22, 2013.

Subsequently the Sponsor submitted a "Request for Final Approval" on December 4, 2012. At that time while there was no substantive change in the application, there were changes in the 30-count blister package (b) (4) The layout of the packages had been under discussions with the Division since the first tentative approval. In that application the Sponsor changed to a new secondary package manufacturer (b) (4) Also included in that application was a brief argument for approval of the application prior to the time that exclusivity of pediatric safety information expires. The Division found the argument inadequate and requested that the Sponsor coordinate the next submission to the expiration of the protected safety information. I noted in my review that additional packaging issues were pending. This was based upon reviews written up to the time of my review. In fact, additional information was provided after my review and all packaging issues were resolved by the time of the issuing of the last tentative approval action letter.

The Sponsor has now submitted a response to the tentative approval. The application has no substantive changes since the last submission when all scientific and administrative issues were determined to be resolved, except that of the date of the expiration of the protected information.

2. CMC/Device

No new changes since last reviewed.

3. Nonclinical Pharmacology/Toxicology

No new changes since last reviewed.

4. Clinical Pharmacology/Biopharmaceutics

No new changes since last reviewed.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

No new changes since last reviewed.

7. Safety

No new changes since last reviewed.

8. Advisory Committee Meeting

Not Applicable.

9. Pediatrics

The reader should refer to this reviewer's first Team Leaders review for waived, defered and required PREA studies.

10. Other Relevant Regulatory Issues

The tentative approval can now be converted to an approval as the expiration date has expired on the aforementioned safety information.

11. Labeling

The Sponsor notes that, except for dates, the Package Insert and MedGuide has not changed since our last Tentative Approval action. This was confirmed with a Word doc-compare.

12. Recommendations/Risk Benefit Assessment

Approval is recommended.

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/s/

NORMAN HERSHKOWITZ
08/15/2013