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APPLICATION NUMBER:

204417Orig1s000

CLINICAL REVIEW(S)

Summary Review

Date	December 18, 2018
From	Philip H. Sheridan, MD
Subject	Summary Review
NDA/BLA # and Supplement#	204417
Applicant	Sun Pharma Advanced Research Company Limited
Date of Submission	July 2, 2018
PDUFA Goal Date	January 2, 2019
Proprietary Name	Elepsia XR
Established or Proper Name	Levetiracetam
Dosage Form(s)	Extended-release tablets 1000 mg and 1500 mg
Applicant Proposed Indication(s)/Population(s)	Adjunctive therapy in the treatment of partial-onset seizures in patients 12 years of age and older with epilepsy
Applicant Proposed Dosing Regimen(s)	Initiate treatment with a dose of 1000 mg once-daily. The once-daily dosage may be adjusted in increments of 1000 mg every 2 weeks, to a maximum recommended daily dose of 3000 mg/day
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/ Population(s) (if applicable)	Adjunctive therapy for the treatment of partial-onset seizures in patients 12 years of age and older
Recommended Dosing Regimen(s) (if applicable)	Initiate treatment with a dose of 1000 mg once daily. The once-daily dosage may be adjusted in increments of 1000 mg every 2 weeks, to a maximum recommended daily dose of 3000 mg/day

1. Background

This submission by Sun Pharma Advanced Research Company Limited (Sun Pharma) is in response to a complete response (CR) letter issued on September 23, 2015, for a 505(b)(2) application for an extended-release formulation of levetiracetam.

The application uses Keppra XR as the listed drug (LD). Keppra XR (levetiracetam extended-release tablets) is approved for adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older, marketed by UCB, Inc., as Keppra XR, in strengths of 500 mg and 750 mg. The current application proposes extended-release levetiracetam tablets in strengths of 1000 mg and 1500 mg (which are not currently available for the listed drug).

The original 505(b)(2) application was submitted in May 2012, and was issued a CR letter on March 29, 2013, because of a discrepancy between the plasma concentration-time curves of Elepsia XR and the LD in the fed state, and because of the potential for dose-dumping identified by *in vitro* testing at the highest alcohol concentration ((b) (4) %). A resubmission of the application on September 1, 2014, adequately addressed the deficiencies cited in the March 2013 CR letter, leading to issuance of an approval letter on March 2, 2015. After issuance of the approval letter, it was recognized that the compliance status of a manufacturing facility was not acceptable at the time of approval. Accordingly, after due consideration and discussion with the applicant, the approval was rescinded on September 23, 2015, and a CR letter was issued on the same day, citing deficiencies identified during facility inspections.

A second resubmission of the application on September 23, 2016, asserted that corrective actions had been implemented and that the facility cited as the basis for the CR was ready for repeat inspection. This resubmission also proposed changes to labeling regarding use in patients with renal impairment. The cited manufacturing facility was inspected from November 17 to December 2016, and it was found to remain unacceptable, resulting in a withhold approval recommendation from the FDA Quality reviewer. In addition, the Clinical Pharmacology reviewer did not accept the applicant's rationale for eliminating the labeling statement that Elepsia is not recommended for use in patients with moderate to severe renal impairment. This decision was communicated to the applicant in a CR letter dated March 22, 2017.

Prior to this new submission, the applicant states that corrective actions were implemented at the cited manufacturing facility. In addition, this new submission includes revised draft labeling, carton graphics, and the addition of a physician sample (b) (4) presentation, as well as additional labeling modifications to align with the LD (Keppra XR) labeling that was approved on October 24, 2017.

2. Product Quality

The Quality Assessment Review by the Office of Product Quality (OPQ) Review Team was summarized by Dr Martha Heimann on Dec 6, 2018.

She notes that the current resubmission documents that all facilities that will be involved in the commercial manufacture and testing of Elepsia (levetiracetam) extended-release tablets are currently acceptable. She further notes that the applicant has proposed minor changes to the formulation of the 1000-mg strength tablet and to the manufacturing process for both (1000 mg and 1500 mg) strengths, as well as the addition of another packaging configuration (b) (4) (b) (4). She concludes that all the CMC drug product information provided in this resubmission is acceptable to support the approval of NDA 204417.

3. Nonclinical Pharmacology/Toxicology

N/A.

4. Clinical Pharmacology

The Clinical Pharmacology review was written by Dr. Hristina Dimova and Dr. Angela Men.

These reviewers note that, in the action letter of March 22, 2017, the applicant was advised that: "*We are unable to include in ELEPSIA XR labeling* (b) (4) (b) (4) (b) (4) and the statement about patients with moderate or severe renal impairment should therefore remain in labeling.

The Clinical Pharmacology review team recommends approval of Elepsia XR.

5. Clinical Microbiology

N/A.

6. Clinical/Statistical-Efficacy

N/A.

7. Safety

N/A.

8. Advisory Committee Meeting

N/A.

9. Pediatrics

N/A.

10. Other Relevant Regulatory Issues

There are no other unresolved regulatory issues.

11. Labeling

Dr. Dhara Shah reviewed the proposed carton and container labeling submitted by the applicant and found them to be acceptable.

Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

12. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
12/20/2018

ERIC P BASTINGS
12/20/2018
I concur, and will issue an approval letter.