

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204417Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA #	204417
Supplement #	
Applicant Name	Sun Pharma Advanced Research Company Limited
Date of Submission	9/2/14
PDUFA Goal Date	3/2/15
Proprietary Name/ Established (USAN) Name	Elepsia XR/levetiracetam (extended release)
Dosage Forms/Strength	Extended release tablets/1000 mg and 1500 mg
Proposed Indication(s)	Adjunctive therapy in the treatment of partial onset seizures in patients ≥ 12 years of age with epilepsy
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	Ed Fisher, PhD
CMC/OBP Review	Elsbeth Chikhale, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Hristina Dimova, PhD
OPDP	N/A
OSI	N/A
CDTL Review	Norm Hershkowitz, MD, PhD
OSE/DMEPA	N/A
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	N/A
PMHS	N/A
SEALD	N/A
Other	N/A

OND=Office of New Drugs
 OPDP=Office of Prescription Drug Promotion
 OSE=Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 CDRH=Center for Devices and Radiologic Health

PMHS=Pediatric and Maternal Health Staff
 DDRE=Division of Drug Risk Evaluation
 DRISK=Division of Risk Management
 OMP=Office of Medical Policy
 DMPP=Division of Medical Policy Programs
 SEALD=Study Endpoints and Labeling Development
 CSS=Controlled Substance Staff

1. Introduction

This submission is an application by Sun Pharma Advanced Research Company Limited (Sun Pharma) for the approval of an extended-release formulation of levetiracetam.

Extended-release levetiracetam is an approved drug for adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older with epilepsy, marketed by UCB, Inc., as Keppra XR in strengths of 500 mg and 750 mg.

Sun Pharma originally submitted the current 505(b)(2) application for a novel extended release tablet in strengths of 1000 mg and 1500 mg based on Keppra XR as the reference listed drug (RLD) in May 2012. That original application was not approved and a complete response (CR) letter was issued to Sun Pharma in March 2013.

This application is supported by reliance on our previous finding of safety and effectiveness for approved extended-release levetiracetam (Keppra XR), clinical pharmacology studies, and manufacturing information.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

As described in the Division's CR letter, issues precluding approval of the original application involved plasma concentration-time curves in the fed state that differed significantly between the proposed product and Keppra XR (they were bioequivalent in the fasted state, and, though in only one of two studies, albeit the positive study was a more well evaluated study, in the fed state), raising concerns about the similarity of safety and effectiveness between the two products, and evidence of alcohol related dose dumping not seen with Keppra XR. Addressing both of these issues in labeling with use limitations was not an acceptable solution given concerns about the potential for medication errors when switching between Keppra XR and the proposed product. Thus, the original application was not approved.

3. CMC/Device

As described by Dr. Chikhale, prior to this resubmission, the applicant submitted additional data concerning the issue of alcohol related dose dumping and, after review, we informed the applicant that there was no further concern in this area and further in vivo studies would not be needed. A biowaiver request for the 1000 mg strength was found acceptable during the first cycle. Dr. Prafull Shiromani reviewed the chemistry and manufacturing information during the first cycle and recommended approval. I concur with the conclusions reached by Dr. Chikhale and Dr. Shiromani regarding the acceptability of the manufacturing of the drug

product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Dr. Fisher reviewed a safety assessment of total daily exposure to polyvinyl alcohol and found no safety concern associated with the daily amount at the highest recommended daily dose. I concur with the conclusions reached by Dr. Fisher that there are no outstanding nonclinical issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Following the CR action, we met with the sponsor and suggested a crossover pharmacokinetic (PK) study evaluating the fed and fasted states with both the proposed product and Keppra XR to address the concerns preventing approval. Given that the differences in plasma concentration-time curves were subjectively not as significant as those typically seen with extended-release and immediate-release antiepileptic drugs, we felt that the most important issue to address was a comparison of the pharmacokinetic parameters, including peak and trough concentrations, of the proposed product and Keppra XR during switches between the fed and fasting states. The sponsor conducted that study and it was reviewed in detail by Dr. Dimova and summarized by Dr. Hershkowitz. As they both describe, this study compared daily switching between the fasted and fed state in healthy volunteers who took each of the products for a 4 day period separated by a 16 day washout. Bioequivalence was demonstrated for the two products under fed conditions, and, although about 20% of the subjects had prolonged absorption of the proposed product when dosed with food, on the following day peak and trough concentrations of the proposed product were similar to those of Keppra XR, and they did not differ significantly from those subjects without prolonged absorption of the proposed product. Accordingly, both Dr. Dimova and Dr. Hershkowitz find that there is no clinically meaningful impact of the difference in absorption between the proposed product and Keppra XR and that the proposed product can be administered without regard to food. Both recommend approval. I concur with the conclusions reached by Dr. Dimova and Dr. Hershkowitz that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Efficacy is addressed by extrapolation from the efficacy of Keppra XR, as described in its labeling, based on support from the PK comparisons described above that established

bioequivalence and addressed observed differences in the plasma concentration-time curves in the fed state. There are no new efficacy data.

8. Safety

Safety parameters in the clinical pharmacology study were reviewed by Dr. Hershkowitz and he found no issues of concern. The safety profile of the proposed product will be informed by the safety profile of Keppra XR, as reflected in its approved labeling. I concur with the conclusions reached by Dr. Hershkowitz that there are no outstanding safety issues that preclude approval.

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

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

13. Decision/Action/Risk Benefit Assessment

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

The sponsor has provided substantial evidence of effectiveness for the use of extended-release levetiracetam for adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older with epilepsy based on extrapolation from the efficacy of Keppra XR, as supported by pharmacokinetic assessment. There are no new safety concerns. There are no outstanding unresolved issues.

There are no necessary postmarketing requirements or commitments.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of extended-release levetiracetam for adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older with epilepsy.

For these reasons, I will issue an approval letter for this application, to include the agreed-upon product labeling.

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/s/

WILLIAM H Dunn
03/02/2015

MEMORANDUM

DATE: March 28, 2013

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 204417

SUBJECT: Action Memo for NDA 204417, for the use of Levetiracetam Extended Release Tablets, 1000 and 1500 mg, as adjunctive treatment for partial seizures (b) (4)

NDA 204417, for the use of Levetiracetam Extended Release Tablets, 1000 and 1500 mg, as adjunctive treatment for partial seizures (b) (4), was submitted by Sun Pharma Global FZE on 5/29/12. Keppra XR, an extended release levetiracetam product, is currently marketed by UCB Pharma (approved in 2008) for the treatment of partial seizures (b) (4). The current sponsor proposes that this NDA be approved under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, referencing the Keppra XR NDA as the Referenced Listed Drug (RLD). It is worth noting that Sun has also submitted applications to the Office of Generic Drugs for 500 and 750 mg strengths of this product (these are the currently approved strengths of the Keppra XR product).

The application contains several bioequivalence/bioavailability (BE/BA) studies designed to demonstrate that the proposed 1500 mg tablet is bioequivalent to 2 X 750 tablets of the currently approved Keppra XR. The sponsor proposes that the 1000 mg tablet be approved on the basis of dissolution data and relevant chemistry information. The application also contains chemistry information, as well as dissolution data, and an in vitro study that examined the potential of alcohol to cause early release of the active moiety ("dose dumping").

The application has been reviewed by Dr. Julie Neshiewat, Office of Medication Error Prevention and Risk Management (DMEPA); Dr. Gopa Biswas, Office of Scientific Investigations; Drs. Hristina Dimova and Atul Bhattaram, Office of Clinical Pharmacology; Dr. Prafull Shiromani, Office of New Drug Quality Assessment (ONDQA); Dr. John Duan, ONDQA, Biopharmaceutics; and Dr. Norman Hershkowitz, neurology team leader, and Cross-Discipline Team Leader. Dr. Hershkowitz recommends that the application not be approved.

In this memo, I will very briefly review the relevant data, and offer the rationale for the division's action.

Briefly, the product is a tablet with an impermeable coat, save for a laser drilled hole at the top. This hole opens onto the first layer of the product, the Explodable layer. Below the Explodable layer is the Drug containing matrix.

When water enters the laser drilled hole, it causes the Explodable layer to swell; eventually, this layer disperses (“explodes”), removing the top of the impermeable coat, and exposing the Drug containing matrix, from which the drug is released.

As described by Drs. Dimova and Hershkowitz, the sponsor has performed three BE studies.

Study PKD_10_130 compared a single 1500 mg tablet to 2 X 750 mg Keppra XR tablets in 18 healthy volunteers in the fasted state. The products were bioequivalent.

Study PKD_10_131 compared the same products in 18 healthy volunteers in the fed state. Although the products met BE criteria for AUC, the 1500 mg tablet had a lower C_{max} than the Keppra product with a 90% CI for the ratio of Test/Reference of (76 to 81).

Because of the failure of the product to meet BE criteria, Sun performed an additional study in the fed state, with more patients.

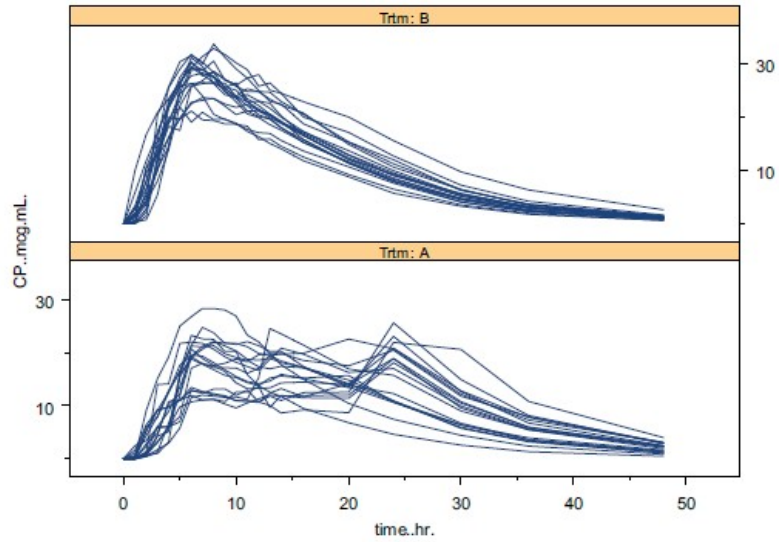
Study PKD_10_272 compared the same products in the fed state in 22 healthy subjects. The products met BE criteria for C_{max} and AUC, the typical requirements for establishing bioequivalence.

However, despite the observation that the two products met BE criteria for C_{max} and AUC in Study 272, examination of the individual plasma concentration-time curves in both fed studies demonstrated that a significant percent of subjects had curves that differed significantly between the two treatments.

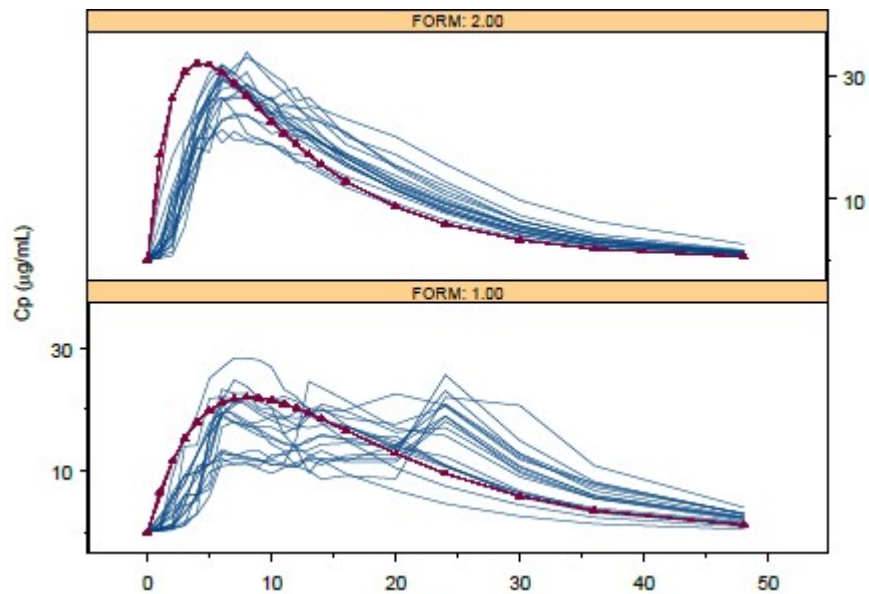
Specifically, 10 subjects in Study 131 and 6 subjects in Study 272 under the 1500 mg tablet treatment arm had a prolonged pattern of absorption compared to Keppra XR, with lower C_{max}'s compared to Keppra, and often resulting in two peaks.

The sponsor attempted to model the comparative curves of the patients with the prolonged absorption pattern at steady state. As Dr. Dimova describes, the predicted shape of the curves at steady state when treated with the 1500 mg tablet did not resemble the predicted shape of the curves for Keppra at steady state.

The following graphs, taken from Dr. Dimova's review, show the curves for the Keppra (top) and Sun products (bottom) from Study 131:

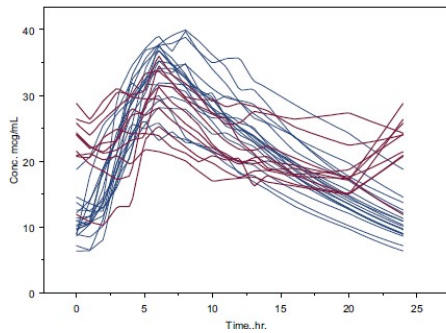


The following graphs, taken from Dr. Dimova's review, show the sponsor's modeled curves (in red) at steady state for the Keppra (top) and Sun (bottom) products, based on the data from Study 131 (observed data in blue):



Dr. Dimova notes that these steady state simulations are unacceptable, because the model does not adequately account for the shape of the predicted curves over time.

The sponsor performed additional simulations to predict steady state curves in the patients with the prolonged release patterns. The following graph, taken from Dr. Dimova's review, displays the Day 5 curves for these patients (Reference-blue curves; Test-red curves):



The sponsor asserts that there should be no concerns about either safety or effectiveness because the trough levels with their product are within the trough levels of those seen in these subjects with Keppra, and also that the trough levels in subjects with their product fall within trough concentrations in responders at 12 hours with Keppra; this last assertion is based on the Clinical Pharmacology review of the Keppra XR NDA.

Alcohol interaction

The sponsor performed an in vitro test examining the release of drug under conditions of varying concentrations of alcohol, a standard assay for extended release products.

The following graph, taken from Dr. Duan's review, shows the effect of alcohol on the dissolution of one batch of drug, demonstrating a clear effect of (b) (4) % alcohol:

Comments

The sponsor has submitted the results of several bioequivalence studies comparing their extended release product to Keppra XR. Although the products are bioequivalent under fasting conditions, and they meet the bioequivalence standards for C_{max} and AUC in one study under fed conditions (Study 272), they failed to meet BE criteria in another study (Study 131) under fed conditions. More importantly, however, in a substantial percent of patients in both studies, the Sun product does not perform the same as Keppra. Specifically, numerous patients have a clearly different pattern of absorption (prolonged, many with two peaks) with the Sun product compared to Keppra in the fed state. Given these significantly different patterns, we cannot be sure that the Sun product will confer similar effectiveness as the Keppra product in the fed state. Although the sponsor asserts that the products should not differ in safety and effectiveness because the trough levels of their product fall in the range of trough levels with Keppra, this observation fails to account for any potential differences between the products with regard to possible safety and effectiveness due to the differences in the absorption patterns in the fed state. Further, the sponsor asserts that trough levels with their product fall in a specific range that they believe has been shown to be associated with effectiveness for Keppra. This statement is based on statements in the Agency's review of the Keppra XR NDA. As Dr. Dimova notes, under the 505(b)(2) mechanism, we are not permitted to examine the Agency's reviews of a RLD; we are only permitted to rely on specific data in approved product labeling. Further, we do not believe that a specific range of trough levels is necessarily associated with effectiveness; as noted

above, the shape of the plasma concentration-time curve is also of considerable importance.

Ordinarily, if a drug does not perform adequately under fed conditions, this can be managed by restricting its use to the fasted state in labeling. However, in this case, such an approach would be problematic. Specifically, Keppra XR can be given with or without food. If we were to approve the Sun product, labeling would need to restrict its use to the fasted state. The existence of two similar products, one whose label permits use with or without food, and one that is restricted to use only in the fasted state, is very likely to be problematic for individual patients. Because it is easy to imagine that patients would be switched between the Sun and Keppra products (given that they will be perceived to be “identical”) it is reasonable to conclude that the conditions of use associated with Keppra (i.e., that it can be given with [or without] food) will be observed for the Sun product, with potential efficacy implications if patients take the Sun product with food. It is difficult to see how the Sun label could be written to reliably prevent this outcome, given that patients may be switched from one product to the other, perhaps frequently.

In addition, in vitro data establish that there is a significant dose –dumping effect of (b) (4) % alcohol on the dissolution profile of the Sun product. Because the sponsor has not performed an in vivo study examining the effects of alcohol on exposure to levetiracetam, labeling would also need to make a statement about a potential interaction with alcohol. Because Keppra has no such statement in its labeling, this poses another risk of medication errors, as described above for this product’s use with food.

For these reasons, then I will issue the attached Complete Response letter.

Russell Katz, M.D.

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/s/

RUSSELL G KATZ
03/29/2013