CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204417Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	2/27/15
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	204417
Applicant	Sun Pharma Advanced Research Company, Ltd.
Date of Submission	9/2/14
PDUFA Goal Date	3/2/15
Proprietary Name / Established (USAN) names	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 (POS) in patients ≥12 years of age with epilepsy
Recommended:	Approval

1. Introduction

The anticonvulsant levetiracetam was first approved for use as adjunctive treatment in partial seizures (POS) in adults in 1999 under the proprietary name of Keppra. Latter submissions extended its use in partial seizures down to the age of one month and to other seizures disorders, including myoclonic seizures in patients with juvenile myoclonic epilepsy in patients 12 years and older, and primary generalized tonic-clonic seizures in patients 6 years of age and older. All regimens of use required twice daily dosing. The Sponsor, who possesses the proprietary rights to Keppra, latter (2008) submitted an application for an extended release formulation of Keppra (Keppra XR) for the treatment of partial seizures in patients 16 years and older, which was approved. This formulation permitted once a day dosing; the immediate release formulation required twice a day dosing. The Approval for the extended release was based upon pharmacokinetic studies demonstrating similar bioavailability to the IR formulation and a single blinded and adequately controlled study demonstrating efficacy and safety. The age of use was later extended to $\geq$ 12 years of age, based upon PK studies alone. This occurred after the initial submission of this NDA.

Sun Pharma Advanced Research Company, Ltd. Had previously (5/24/12) developed an XR tablet using what they refer to as "Wrap Matrix" technology. At that time the Sponsor submitted two tablet strengths, 1000 mg and 1,500 mg, for review for the indication of partial seizures in patients (b) (4), based upon a comparison to Keppra XR (the reference labeled drug, RLD) using the 505b2 regulation. They had also submitted lower strengths (500mg and 750mg) to OGD for review as a generic. Keppra XR is considered the RLD. A search using http://dailymed.nlm.nih.gov/dailymed/about.cfm revealed 3 levetiracetam XR formulations presently available in generic form[1]. The generic was approved. But, this division responded with a complete response (CR) action to the proprietary formulation (see the Background section).

2. Background

A CR response was taken on the original submission because:

- While Sponsor's 1500 mg the tablet showed bioequivalence to the reference product during fasting, the Cmax was just outside the criteria for bioequivalence in one study during the fed state. A repeat fed study, however, did demonstrated bioequivalence for Cmax, as well as other indices. However, a third of patients in such studies exhibited a flattening of their absorption curves during the fed state, as compared to fasting. This change in the shape was deemed to be an important factor in the therapeutic profile of this drug, with a particular concern being that the switching back and forth from fed to

[1] The Sponsor's include: Apotex Corp., Golden State Medical Supply, Inc, and Anchen Pharmaceutical, Inc. This search revealed somewhat different information received from word of mouth by other Divisions noting that there are generics pending.

fasting, or visa-versa, could result in in a variation in the Cmax and Cmin values. One solution may have been to label for fasting, but as there is no such restriction on all the other levetiracetam tablets (generic and proprietary), it was believed that such restriction may led to medication errors. At a subsequent end of review meeting the sponsor was provided with the recommendation that this issue might be explored by comparing the pharmacokinetic profiles following switch overs between fed and fasting administration for the RLD and their proposed formulation. The sponsor has now provided such a study.

- Based upon *in vitro* studies, which demonstrated an interaction with a (b)(4)% ethanol solution, the ONDQA reviewer suggested the possibility of dose dumping. He noted that this can approached by either performing a clinical study to elucidate the clinical process and/or by providing labeling instructions not to use with alcohol. Labeling restrictions, however, raises similar problematic issues alluded to regarding dosing in the fed state. To respond to this the sponsor had provided additional information at a time prior to the official submission of this response to a CR action (2/23/13).

3. CMC/Device

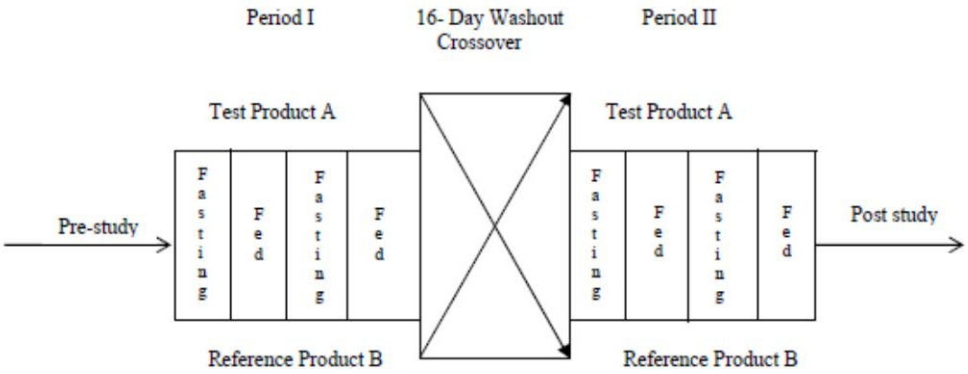
Additional information was provided which responded to the dose dumping issue in a separate prior submission (2/23/13). This information was in the form of additional published reports and *in vitro* dissolution studies with alcohol under various conditions. The ONDQA reviewer determined that dose dumping need not be considered and no additional formal *in vivo* studies are required.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Biopharmaceutics

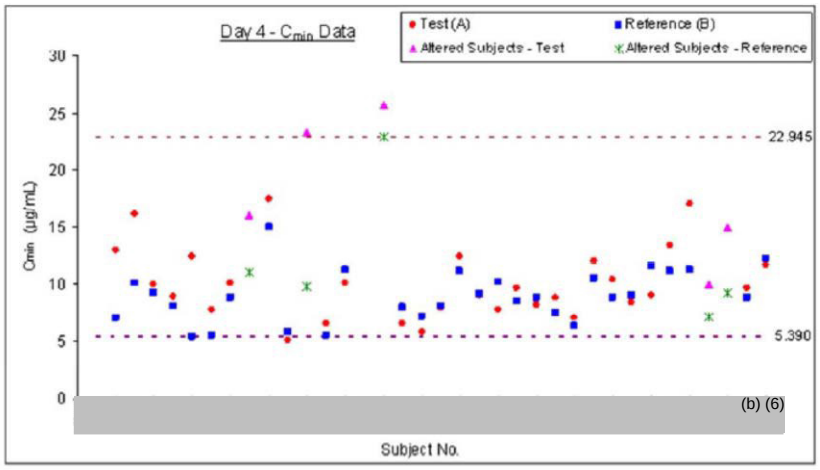
Dr. Dimova performed the pharmacokinetic review. The new study examined relative bioavailability in normal healthy volunteers, 18 to 45 years old, following multiple consecutive daily switching between fasting and fed state in both the RLD and sponsor's formulation. The study consisted of two 4 day periods (Period I and Period II) with a two week washout between each period. Each 4 day period exposed patients to alternating fed and fasting administration of only one of the two formulations. Each patient would than crossover during the next period to a similar fed-fasting alternation using the other formulation. The 1500 mg test product was compared to two 750 mg tablets of the RLD. Thirty four patients were studied. A diagram of this experimental paradigm is presented below. Each box represents a single day.



In Dr. Dimova's words this is study:

> "The results of this study demonstrated that the ratios of the least-square means (and 90% confidence intervals) of the Test to Reference product for LEV after day 2 and day 4 of dosing (i.e day on which subjects were switched from fasting to fed condition) were within the BE limits for AUC0-24 and Cmax under fed condition, In addition, even though about 20% of the subjects in the study had a "prolonged pattern of release" following administration of the Test ER Tablets with food, this did not result neither in potentially sub-therapeutic concentrations nor higher peak concentrations than that of the reference product when subjects were dosed on the following day."

Another way to view this data is to examine scattergrams where single patients Cmax and Cmin data for both products are presented for all 4 days. Upon examination the pharmacokinetic values appear to overlap between both products. One example from Dr. Dimova's review is presented below; i.e. the figure shows Day 4 of Cmin for subjects on the sponsor's formulation and the RLD (note "altered subjects" appears to represent those patients with complex test compound absorption curves).



Dr. Dimova concluded that the label need not specify that the product is to only be used in the fasting condition. It should be noted that the 1,000 mg tablet was previously granted a biowaiver, and therefore this conclusion applies for both the 1500 and 1000 mg tablet. I agree with all the above conclusions.

In the initial submission of this NDA the sponsor asked for approval of age (b) (4) (b) (4). Since that time the RLD had the indication for POS extended down to age 12 years of age based upon PK studies. While the present and previous studies on the test product, Elepsia, examined adult patients, Dr. Dimova believes that the indication can extend down to 13 years age. This has been discussed with Dr. Dimova and constitutes a misreading of the label. She and I agree that the age cutoff should be ≥12 years of age.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Not applicable as conclusions are based upon a pharmacokinetic comparison.

8. Safety

No new pertinent safety information was observed in the new PK study. There were no deaths, SAEs or discontinuations in the new pharmacokinetic study. Safety conclusions will be based upon a pharmacokinetic comparison to the RLD.

9. Advisory Committee Meeting

None.

10. Pediatrics

Not applicable as this is not a new formulation: i.e. once a day extended release formulation is already available.

11. Other Relevant Regulatory Issues

Dr. Dimova noted that GLP Compliance Office of Scientific Investigations recommended accepting data for NDA 204417 resubmission without on-site inspection of the clinical and bioanalytical sites for the new studies based on the satisfactory inspections in recent years and similarity of the methodologies and processes in the previous submission.

The name Elepsia XR was reviewed and found acceptable.

12. Labeling

Final label agreed upon by the sponsor and Division. Please see approval letter.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval for both the 1,000 mg and 1500 mg tablet. No restriction for feed state is required in the label.
- Risk Benefit Assessment: Acceptable and not different form the RLD.
- Recommendation for Postmarketing Risk Management Activities: None.
- Recommendation for other Postmarketing Study Commitments: None.
- Recommended Comments to Applicant: None.

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

/s/

NORMAN HERSHKOWITZ
02/27/2015

Cross-Discipline Team Leader Review

Date	3/28/13
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	204417 (000)
Applicant	Sun Pharma Advanced Research Company, Ltd.
Date of Submission	May 24, 2012
PDUFA Goal Date	3/29/13
Established (USAN) names	Levetiracetam Extended-Release
Dosage forms / Strength	Extended release teblets/1000 mg and 1500 mg
Proposed Indication(s)	Adjunctive therapy in the treatment of partial onset seizures in patients ≥ (b) (4) years of age with epilepsy
Recommended:	Complete Response

1. Introduction

The anticonvulsant levetiracetam was first approved for use as adjunctive treatment in partial seizures in adults in 1999 under the proprietary name of Keppra. Latter submissions extended its use in partial seizures down to the age of one month and to other seizures disorders, including myoclonic seizures in pateints with juvenile myoclonic epilepsy in pateints 12 years and older, and primary generalized tonic-clonic seizures in pateints 6 years of age and older. All regimens of use required twice daily dosing. The Sponsor, who possesses the proprietary rights to Keppra, latter (2008) had an extended release formulation of Keppra approved for the treatment of partial seizures in patients 16 years and older. This formulation permitted once a day dosing; the immediate release formulation required twice a day dosing. The Approval for the extended release was based upon pharmacokinetic studies demonstrating similar bioavailability to the IR formulation and a single blinded and adequately controlled study demonstrating efficacy and safety.

Sun Pharma Advanced Research Company, Ltd. has now submitted an XR tablet using what they refer to as "Wrap Matrix" technology. The Sponsor is submitting two tablet strengths, 1000 mg and 1,500 mg for review for the indication of partial seizures in pateints (b) (4), based upon a comparison to Keppra XR using the 505b2 regulation. They have also submitted lower strengths (500mg and 750mg) to OGD for review as a generic. Keppra XR is considered the RLD. A search using http://dailymed.nlm.nih.gov/dailymed/about.cfm revealed 3 levetiracetam XR formulations presently available in generic form[1].

2. Background

Upon the first development of an extended release formulation, when an immediate formulation is already marketed, this division usually requires a demonstration not only the similarity of bioavailability, but a single adequate, well controlled and blinded efficacy/safety trial. The presumption in this case is that although normal standards of bioavailability may be similar, the shape of the absorption curve may result in a different efficacy/safety profile. In the case of the present product, however, an existing extended release product is already available, and may be used for simple bioavailability comparison. The Sponsor accordingly followed this strategy in product development. There were, however, complications to this development scheme, as will be noted below.

[1] The Sponsor's include: Apotex Corp., Golden State Medical Supply, Inc, and Anchen Pharmaceutical, Inc. This search revealed somewhat different information received from word of mouth by other Divisions noting that there are generics pending.

3. CMC/Device

Dr. Shiromani performed the CMC issue. In reviews completed on 2/28/13 and 3/12/13, Dr. Shiromani concluded that the application can be approved based upon CMC considerations. Of note, all inspections were found adequate. The ONDQA reviewer, however, identified an issue that will be discussed in the Clinical Pharmacology section, as it relates to a problematic Pharmacokinetic issue.

4. Nonclinical Pharmacology/Toxicology

Not Applicable.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Dimova performed the Pharmacokinetics review and Dr. Duan the ONDQA review.

As noted above, proof of efficacy was to be based upon a demonstration of bioequivalence between the RLD, Keppra XR, and the Sponsor's levetiracetam ER Tablets formulation. The Sponsor used 3 single-dose, randomized, open-label, crossover bioequivalence (BE) studies to compare their final proposed 1500 mg tablet formulation to the RLD, Keppra XR® Tablets (2 x 750 mg) in healthy adult subjects under fasted and fed conditions.

When examined under fasting conditions, the Sponsor's tablet proved to be bioequivalent, by normal standards (see table transcribed from the PK review below).

Fasted Study PKD_10_130 (n=18)

Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV%	P-value [4]
	Test	Reference	Test	Reference				
AUC_{0-t}	5.96	5.98	388.00	396.97	97.74	83.40 to 114.54	27.77	0.8045
AUC_{0-inf}	5.98	6.01	396.24	405.68	97.67	83.27 to 114.56	27.93	0.7999
C_{max}	3.10	3.15	22.25	23.22	95.84	81.80 to 112.27	27.71	0.6453

[4]P-value is for product effect

An initial study that examined bioequivalence under feed condition, failed to show bioequivalence (see table transcribed from the PK review below). Thus, the Cmax was below the geometric least square mean ratio of Test/Reference of 0.8 and 1.25.

Fed Study PKD_10_131 (n=18)

Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV%	P-value [4]
	Test	Reference	Test	Reference				
AUC_{0-t}	6.18	6.22	484.86	501.74	96.64	92.74 to 100.69	7.07	0.1655
AUC_{0-inf}	6.23	6.24	507.96	515.02	98.63	94.28 to 103.17	7.75	0.6001
C_{max}	3.09	3.33	21.93	27.88	78.67	75.96 to 81.47	6.03	<0.0001

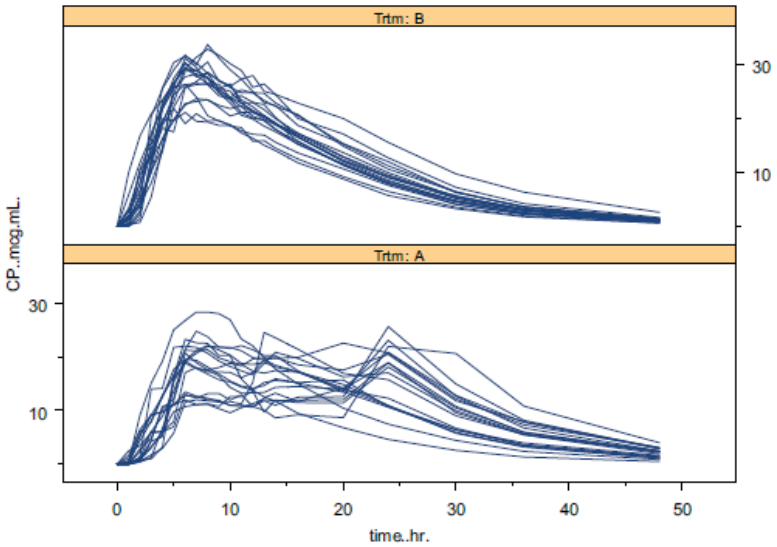
Because of the latter finding of the absence of bioequivalence, the Sponsor performed a repeat fed study in a larger population (n=22), and according to Dr. Dimova, the Sponsor omitted earlier sampling time points and added additional time points at the later part of the plasma concentration profile. This analysis indicated bioequivalence (see table transcribed from the PK review below).

Fed Study PKD_10_272 (n=22)

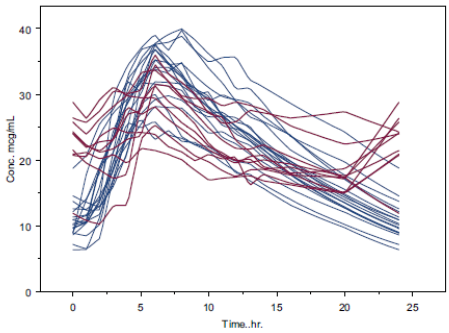
Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV%	P-value [4]
	Test	Reference	Test	Reference				
AUC_{0-t}	6.16	6.14	475.30	466.37	101.92	95.05 to 109.27	13.41	0.6439
AUC_{0-inf}	6.20	6.17	491.76	478.40	102.79	95.87 to 110.22	13.41	0.5035
C_{max}	3.22	3.26	25.03	26.00	96.27	87.65 to 105.75	18.12	0.4931

An observation noted by Dr. Dimova in both fed studies was, unlike absorption curves for the RLD, or absorption curves for the Sponsor's test product in the fasting state, the shape of the absorption curve did not show a simple monotonic peak, but revealed a flattened appearance or a second peak in about one-third of the subjects. An example of this is presented in the figure below (transcribed from the PK review). This figure compares the single dose fed absorption curves for the RLD (TRTM B, Keppra XR) and the Sponsor's product (TRTM A).

Levetiracetam plasma concentration-time profiles in the fed pivotal study PKD_10_131 (Trtm A: Test formulation, Trtm B: Reference formulation)



In order to better examine this the Sponsor was asked to provide a number of simulations at steady state. The sponsor provided simulations by the superposition method of plasma concentrations for subjects in the test product arm who showed "prolonged pattern of release" in the fed state from study PKD-10-131 with the RLD from studies on Days 2, 3, 4, and 5 administrations. Dr Dimova notes that the final comparison of the RLD with simulations shows a distinctly different shape when the two drugs are compared. Moreover, Cmax were smaller and the trough higher on average for the test product in the simulations as compared to the RLD. The AUCs, according to Dr. Dimova, however, were comparable. This is presented in the figure below for Day 5 of the simulation; the blue curves represent the reference product and the maroon the test product.



Dr. Dimova concludes that because of the difference in the shapes of the absorption curves, when simulations at steady state are performed for the one-third of the aberrant absorption group in the fed state, and the absence of information as to how the shape of such curves factor into pharmacodynamics, one must conclude that the test and RLD compounds may have different properties with regard to safety and efficacy. The Sponsor argues that this modeling should adequately support the approval because the range of troughs for the test product under fed conditions fall in the range of that observed for troughs of the RLD. This, however does not speak to the issues of the shape of the curve. The importance of the shape of the curve is a

principal that the Division has always espoused, as described above, and is one of the reasons that the division requires efficacy study for the development of the first release formulation (see the Background sections). This reviewer concurs with Dr. Dimova's conclusion. As a result of this Dr. Dimova recommends that this product should be labeled to be taken in a fasting state. This creates other problem in medication errors, which are described below.

I would further add that this issue is complicated by the fact that patients will likely be switching from fasting to fed or fed to fasting as part of alterations in daily routine. This may have an effect to result in transient alterations in peaks and troughs at such transitions which may alter the level of seizure control or adverse reactions. The Sponsor was asked to model these scenarios, but was unable to do so.

The ONDQA reviewer determined that 1,000 tablet strength could be approved based upon dissolution studies; however acceptance criteria to 4 hours should be revised. However, based upon in vitro studies, which demonstrated an interaction with a (b)(4)% ethanol solution, Dr. Duan suggested the possibility of dose dumping. He noted that this can approached by either performing a clinical study to elucidate the clinical process and/or by providing labeling instructions not to use with alcohol. Labeling restrictions, however, raises similar problematic issues alluded to regarding dosing in the fed state. This will be further discussed below.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical- Efficacy

Not applicable as conclusions are based upon a pharmacokinetic comparison.

8. Safety

Not applicable as conclusions are based upon a pharmacokinetic comparison.

9. Advisory Committee Meeting

None requested.

10. Pediatrics

Not applicable as this is not a new formulation: i.e. a once a day extended release formulation is already available.

11. Other Relevant Regulatory Issues

The DMEPA reviewer was Julie Neshiewat. While DMEPA had a number of labeling and packaging recommendations these will not be discussed in this review because of a more important overarching issue. The DMEPA reviewer notes that considering that the RLD as well as future generic products are/will not be labeled to be taken only during fasting, which the present product requires (see above), may result in medication errors. As noted above, this reviewer has identified 3 presently manufactured generics without this labeling requirement as well. This is further complicated by the fact that 2 lower strengths to be marketed by the manufacturer as a generic will not have this stipulation.

Lastly, the RLD and other extended release products and the Sponsors lower does have no restrictions not to be taken with alcohol because of potential dose dumping effect. This, again, can lead to a similar problem with medication errors.

12. Labeling

Deferred as per the CR action.

13. Recommendations/Risk Benefit Assessment

As noted above the present product will require dosing restriction in the label that will be unique to this formulation. Because this will be the only product where such labeling is required, it is the opinion of the reviewer, as well as DMEPA, that there will be a likelihood that such restriction will not be followed. Not following these restrictions can lead to inadequate efficacy and the occurrence of adverse reactions, depending upon the conditions of administration (fed/fasting, with/without alcohol). Consequently this reviewer recommends a CR action.

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

/s/

NORMAN HERSHKOWITZ
03/28/2013