CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-285

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	9/10/08
From	Billy Dunn, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22285
Applicant	UCB, Inc.
Date of Submission	11/13/07
PDUFA Goal Date	9/14/08
Proprietary Name / Established (USAN) names	Keppra XR/Levetiracetam (extended release)
Dosage forms / Strength	500 mg tablet
Proposed Indication(s)	Adjunctive therapy in the treatment of partial onset seizures
Recommended:	Approval

1. Introduction

Keppra is an approved drug product for the treatment of multiple forms of epilepsy.

This submission is a new NDA for an extended release preparation of levetiracetam (Keppra XR) that is manufactured using the same drug substance as the currently approved product.

The review team for this NDA included the following reviewers:

Chemistry – David Claffey, PhD
Clinical Pharmacology – Gilbert Burckart, PharmD
Statistics – Jingyu Luan, PhD
Clinical – Martin Rusinowitz, MD

I discuss below the key conclusions of each reviewer and provide my recommendations regarding this submission.

2. Background

Keppra is an approved anticonvulsant. It is thought to have a unique mechanism of action. It was originally approved in 1999 and has had several follow-on approvals for additional doses, formulations, and indications. It is currently indicated for adjunctive therapy in the treatment of partial onset seizures in adults and children with epilepsy 4 years of age and older. Additional indications have been granted (myoclonic seizures, generalized tonic-clonic seizures) and multiple formulations exist (immediate release tablet, oral solution, injection).

Current doses marketed as immediate release tablets include 250 mg, 500 mg, 750 mg, and 1000 mg with a labeled therapeutic dosage of 1000-3000 mg/day in adults 16 years of age and older.

This NDA is for Keppra XR, an extended release preparation of the same drug substance in a 500 mg tablet. The sponsor seeks an indication for the adjunctive treatment of partial onset seizures in patients [redacted] years of age and older. The product is proposed in order to enhance convenience and compliance. There is the first NDA submission for this product and it is not approved elsewhere. b(4)

The clinical development program for Keppra XR consisted of five studies, four in healthy subjects. The first study was a regional absorption study and did not use the Keppra XR tablet. Three clinical pharmacology studies were conducted in healthy volunteers. One efficacy and safety study was conducted in epilepsy patients.

Two meetings with the sponsor took place. The first was a pre-IND meeting on 4/19/06 and the second was a pre-NDA meeting on 10/1/07. There are no significant outstanding issues from these meetings.

3. CMC/Device

The drug substance is levetiracetam, as approved in Keppra tablets. All CMC information was cross referenced to the approved NDA. The drug product is an extended release tablet. There are no issues with inactive ingredients. Stability data are acceptable with a 24-month expiration date. Inspections have been completed and are acceptable. There are no unresolved CMC issues. Dr. Claffey recommends approval.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

Three clinical pharmacology studies (N01140, N01160, and N01260) were conducted in healthy volunteers to investigate the bioavailability of the extended release tablet 500 mg as compared to the immediate release tablet 500 mg, the food effect, and the dose proportionality over the approved 1000 mg to 3000 mg dose range for immediate release Keppra.

Study N01140 tested three formulations of extended release tablets (in comparison to the same dose of immediate release Keppra) in 12 healthy subjects and all were found to be similar.

Study N01160 was a pivotal randomized three way crossover study in 24 healthy subjects of Keppra immediate release 500 mg tablets versus Keppra XR 1000 mg (two 500 mg tablets) administered as a single dose and as multiple doses while fasting, along with a study after a meal. Time to peak was delayed by approximately 3 hours after administration of XR tablets in comparison to the administration with IR tablets. No relevant difference in the other PK parameters was found. The study demonstrated comparable Cmax and AUC but a lower Cmin (approximately 26%) for Keppra XR compared to Keppra immediate release tablets: Bioequivalence was not strictly demonstrated in multiple dose administration as the lower 90% CI limit of the Cmax ratio (XR/IR) was marginally below the 80% - 125% bioequivalence range (79.13%). Food did not have a significant effect upon Cmax or AUC.

Study N01260 demonstrated dose proportionality with Keppra XR at 1000, 2000, and 3000 mg in 24 healthy subjects.

In the efficacy and safety study (N01235) mean trough concentrations for patients having at least two levels on the 1000 mg/day dosage was 77% higher in 6 adolescent subjects (age 12-16, the only patients of this age group treated with Keppra XR in the study) than in the adults. In addition, Hispanic patients had 40% higher trough concentrations than did Caucasian patients. Geriatric patients (over age 65) were essentially unstudied, as only one geriatric patient received Keppra XR. No other relevant clinical pharmacologic results were generated in this study.

Other clinical pharmacologic considerations refer to the original Keppra NDA. There are no QT concerns with Keppra. Keppra is rapidly and almost completely (>95%) absorbed following oral ingestion with a Tmax of 1.3-5.2 hours. The mean half-life of Keppra in serum is 6–13.3 hours. Keppra enters the cerebrospinal fluid with a Tmax of 3–7.3 hours. Efflux of Keppra from the CSF takes twice as long as that from the blood (t1/2 of 24 hours). Metabolism of Keppra is minimal, and excretion occurs almost completely through urine. Approximately 34% of the administered dose of Keppra is metabolized and 66% is recovered unchanged in urine. Keppra's clearance is in relation to creatinine clearance, with over 90% of the drug being excreted within 48 hours. Keppra and its major metabolite, which is inactive, are less than 10% bound to plasma proteins. Differences in pharmacokinetics based upon body weight and renal function can be seen in women (20% higher AUC than men), pediatric patients (40% higher body-weight adjusted clearance), and severe hepatic impairment (clearance 50% of normal, mostly secondary to decreased renal function). Total body clearance is decreased by 38% and the half-life is 2.5 hours longer in the elderly compared to healthy adults. Dose dumping with alcohol was not seen in vitro.

Dr. Burckart has several recommendations:

- Approval only be granted for use in adults age 16 and older
- Keppra XR not be recommended for use in dialysis dependent end stage renal disease patients
- A phase 4 commitment to perform a pharmacokinetic study in geriatric patients

- [redacted] b(4)
- Labeling changes consistent with his review and recommendations

In the context of these recommendations, Dr. Burckart recommends approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

As discussed during the pre-IND and pre-NDA meetings, the sponsor conducted a single efficacy and safety study (N01235). This was a phase 3, placebo-controlled, randomized (1:1), parallel group, double-blind, multi-center, add-on study to evaluate the efficacy, safety and tolerability of Keppra XR 2x500 mg/day once daily in refractory epilepsy patients 12 to 70 years of age with partial onset seizures treated with at least one but no more than three concomitant antiepileptic drugs. Of 188 patients screened, 158 were randomized (130 were planned) into the study by 34 investigators in 7 countries, including Brazil, Finland, India, Mexico, Russian Federation, South Africa, and Ukraine. 59 females and 99 males aged 12.2 to 67.9 years were enrolled and represented the intent to treat (ITT) population. Of these 79 were in each group (placebo and active). 143 patients (72 placebo, 71 active) completed the study. The study duration per patient was approximately 22 weeks consisting of an 8-week baseline period (during which the patient had to have at least 8 partial seizures) followed by a 12-week treatment period with Keppra XR or placebo with a final visit occurring at week 22.

The primary efficacy variable was the partial onset seizure frequency per week over the treatment period. The treatment difference was expressed as a percent reduction over placebo. This analysis was performed on the ITT population. Secondary endpoints included total seizure frequency per week, the responder rate (proportion of patients with a 50% or greater reduction in seizure frequency per week from baseline) for partial onset seizures, the responder rate for total seizures, the categorized response (percent reduction) for partial onset seizures, and the categorized response for total seizures.

The demographics between treatment groups were reasonably well matched. Placebo patients were younger at diagnosis of epilepsy and had a longer duration of epilepsy. Baseline seizure types were similar.

Dr. Luan's review includes the sponsor's table listing the primary efficacy results and is reproduced below.

Table 4: Partial Onset Seizure (Type I) Frequency per Week (ITT Population)

Period	Statistics	PBO N=79	LEV XR N=79
Baseline Period	n	79	79
	Mean (SD)	3.73 (6.57)	4.87 (8.23)
	Median	2.11	1.80
	Q1 - Q3	1.33 - 3.26	1.13 - 4.13
	Min - Max	1.0 - 53.5	0.0 - 47.3
Treatment Period	n	78	75
	Mean (SD)	2.77 (4.64)	3.27 (5.98)
	Median	1.36	0.99
	Q1 - Q3	0.92 - 2.85	0.33 - 2.70
	Min - Max	0.0 - 33.9	0.0 - 29.1
% Reduction from Baseline Period	n	78	74
	Mean (SD)	19.33 (51.75)	42.65 (48.54)
	Median	33.40	46.07
	Q1 - Q3	-6.63 - 51.81	22.95 - 76.86
	Min - Max	-199.0 - 100.0	-210.5 - 100.0

Source: Table 14.2.1:1

The percent reduction of Keppra XR over placebo in seizure frequency per week was 14.4% for the ITT population ($p = 0.038$). This increased to 18.6% ($p = 0.003$) after excluding the subjects with major protocol deviations as specified in the protocol [10 subjects (12.7%) in the placebo group; 11 (13.9%) in the Keppra XR group]. The result for total seizures was similar for the ITT population at 14.7%. The responder rate for partial onset seizures favored Keppra XR (43.0% vs. 29.1%) as did that for total seizures (43.0% vs. 30.4%). Both partial onset and total seizure frequency demonstrated a larger categorical very positive (75% or greater) response for Keppra XR.

Dr. Luan performed several additional analyses to confirm the efficacy of Keppra XR. As the log-transformed primary efficacy endpoint was still not normally distributed she conducted the Wilcoxon Rank Sum Test for the original primary efficacy endpoint. The result remained statistically significant at a two-sided 0.05 level ($p=0.0372$). She compared the baseline seizure frequency per week and found that they were not significantly different ($p=0.42$). As the protocol was planned for 130 patients but randomized 158 subjects, she conducted the primary efficacy analysis on the first 130 enrolled patients and found that the results were consistent.

Both Dr. Luan and Dr. Rusinowitz feel that study N01235 demonstrates the benefit of Keppra XR as adjunctive therapy in the treatment of refractory epilepsy patients 12 to 70 years of age with partial onset seizures.

8. Safety

In the four studies reviewed above that examined Keppra XR, a total of 137 unique subjects were exposed to active study drug, including 77 patients with epilepsy. Given the prior experience with levetiracetam, this represents an adequate safety database for Keppra XR. There is no foreign or postmarketing experience.

In study N01235, one death occurred in a Keppra XR treated patient. The subject died 65 days after study drug initiation due to severe pulmonary bronchiectasis. The subject had a history of pulmonary complaints ("breathlessness") and was treated with theophylline and other unknown medications which were apparently discontinued during the study. Dr. Rusinowitz feels this event is unlikely to be related to the study drug, and I agree.

Including the above death, 8 serious adverse events (SAEs) occurred in study N01235. Two were in placebo patients. Of the 5 remaining SAEs, 2 patients experienced worsening seizures, one experienced skin rash, one experienced ischemic stroke, and one experienced a concussion. The narratives for the concussion and one of the worsened seizures ("repeating simple seizures") could not be located. Both patients with worsened seizures developed recurrent simple partial seizures some time after beginning Keppra XR, at day 17 and day 25 after first dose. The patient with ischemic stroke had multiple vascular risk factors and previous stroke. The patient with skin rash had a history of allergic reactions to at least two previous anticonvulsants, and her rash was felt to be consistent with such an episode. Her rash began about eight hours after her first dose of Keppra XR, and although she developed mouth ulcerations along with the diffuse skin rash, a diagnosis of Stevens-Johnson Syndrome was not felt to be consistent with her time course. She was treated symptomatically and fully resolved.

There were no SAEs in the clinical pharmacology studies.

5 Keppra XR patients (including the patient who died) discontinued study N01235 due to adverse events (8 discontinued total) as compared to 2 placebo patients (7 total). Adverse events in Keppra XR patients leading to discontinuation included asthenia (at day 73), death, aggravated epilepsy, and skin rash. There were no discontinuations due to adverse events in the clinical pharmacology studies.

The overall incidences of adverse events (AEs) between the two groups in study N01235 were similar (125 AEs in 43 placebo patients, 118 AEs in 41 Keppra XR patients). Influenza, irritability, somnolence, and an aggregate of asthenia and fatigue, were all reported more frequently in the Keppra XR group. Otherwise, there were no significant differences. AEs occurring in more than 5% of Keppra XR patients (range 5.2%-7.8%) included headache, influenza, nasopharyngitis, somnolence, nausea, dizziness, and irritability.

There is no evidence of a difference in seizure exacerbation between the placebo and Keppra XR groups. In addition, the sponsor provided historical data to compare Keppra XR with Keppra 500 mg b.i.d. and found no difference in epilepsy-related AEs.

There were no significant differences between groups in clinical laboratory tests.

Overall, the adverse events seen with Keppra XR do not suggest a significant difference from Keppra.

Dr. Rusinowitz finds nothing in his review of the safety data to argue against approval.

9. Advisory Committee Meeting

N/A

10. Pediatrics

PREA requires all applications (or supplements to an application) submitted under section 505 of the Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the Act).

This product represents a new dosage form. The efficacy and safety study enrolled patients as young as 12 years. The Pediatric Review Committee (PeRC) has reviewed this application and has waived the requirement for assessment in the 0-12 age range. The PeRC found the data supporting the use of Keppra XR in the 12-16 range inadequate and has requested the sponsor submit an acceptable pediatric plan for postmarketing assessment in this age range as a condition of approval. The sponsor has submitted an acceptable pediatric plan.

11. Other Relevant Regulatory Issues

N/A

12. Labeling

The proposed label for Keppra XR is informed by the labels of the currently approved Keppra products, with appropriate changes.

Dr. Burckart has recommended several changes to the proposed labeling. Highlights include:

- An increase in the lower indicated age to 16
- Use of immediate release Keppra in dialysis dependent end stage renal disease patients
- Relevant pharmacokinetic updates

Dr. Rusinowitz has not recommended any additional changes.

I recommend addition of the following statement to the end of the Clinical Studies section:

> "The relationship between the effectiveness of the same daily dose of Keppra XR and immediate release Keppra XR has not been studied and is unknown."

The tradename review by DMEPA is complete and recommendations may be found in their review. There are no obstacles to approval.

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

13. Recommendations/Risk Benefit Assessment

I recommend approval of this application.

Although the benefit of Keppra XR does not seem to be as robust as Keppra based on the trial data at hand, the efficacy trial did meet its endpoint. In addition, this trial examined only one dose and had a limited number of patients. Given the identical drug substance and lack of a pharmacokinetic reason for decreased efficacy, it is reasonable to conclude that real-world experience with Keppra XR will likely closely resemble that seen with Keppra.

The safety profile of Keppra XR appears largely consistent with that of Keppra. I do not feel there are any safety signals that warrant disapproval of this application. Perhaps the most concerning safety event, an acute rash with a distinct temporal relationship to exposure to Keppra XR, appears likely to be an idiosyncratic allergic response in a patient predisposed to such events. Rashes were also reported in very small numbers with Keppra. The prompt resolution of the rash with conservative treatment in this case is reassuring. The death that occurred in this study does not appear to be related to the drug, nor does the stroke. Other adverse events that occurred appear acceptable.

I do not feel that specific postmarketing risk management activities are required.

I do not agree with Dr. Burckart's recommendation for a postmarketing study commitment to perform a geriatric pharmacokinetic study. While specific geriatric data was not provided in these studies, extensive experience exists with Keppra (as well as other drugs) that will inform the use of Keppra XR in the general population.

I recommend a postmarketing study requirement for the sponsor to conduct a clinical pharmacologic study in the 12-16 age range, consistent with the comments of the PeRC. The sponsor has submitted an acceptable pediatric plan which has been reviewed and approved by the PeRC, and consistent with this, the following postmarketing study requirement should be communicated to the sponsor in the approval letter:

"You must conduct an open label, single dose, pharmacokinetic study with Keppra XR in patients with epilepsy, ages 12-16 years, in comparison to adult patients with epilepsy. The patient population can presently be receiving Keppra. The pharmacokinetic study would include at least 6 pharmacokinetic samples. The comparison group will be an equal number of adult patients studied under the same conditions.

For each group (adolescents and adults), the mean Cmax and AUC must be estimated with a standard error of 20% or less, and this would be the basis for the original sample size calculation. As study data are evaluated, the sample size can be re-assessed if necessary for precise estimation of these pharmacokinetic parameters.

You must commit to provide the protocol for this pharmacokinetic study within 6 months of approval of Keppra XR (by [redacted] 2009), to initiate the study within 6 months from protocol submission (by September 2009), and to provide the clinical study report within 4 years from study initiation (by September 2012)." b(5)

[redacted] b(4)

[redacted] The sponsor should also be informed of the labeling changes recommended by Dr. Burckart, with which I agree, as well as the addition to labeling I recommend above. [redacted] b(4)

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/s/

William Dunn
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