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APPLICATION NUMBER:

207958Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review (Addendum)

NDA#	207958
Date of Original Submission:	10/1/14
Date of Original OCP Review:	6/5/15
Brand Name:	Spritam
Generic Name:	Levetiracetam (b) (4)
Strength and Formulation:	Tablets: 250, 500, 750 and 1000 mg
Sponsor:	Aprecia Pharm.
OCP Review Team:	Bei Yu, Ph.D., Angela Men, M.D., Ph.D., Kevin Krudys, Ph.D.

The purpose of this review addendum is to address dosing of SPRITAM for primary generalized tonic-clonic seizures in pediatric patients ages 6 to (b) (4).

RECOMMENDATION

We recommend that the SPRITAM label include the following language to provide tablet dosing for primary generalized tonic-clonic seizures in pediatric patients 6 to (b) (4) age:

2.4 Primary Generalized Tonic-Clonic Seizures in Patients 6 Years of Age and Older

Adults and Pediatric Patients 16 Years of Age and Older

Initiate SPRITAM with a dose of 1000 mg/day, given as twice daily dosing (500 mg twice daily). Increase the dosage by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg/day has not been adequately studied.

Pediatric Patients (6 (b) (4) years, and weighing 20 kg to 40 kg)

(b) (4) initiate (b) (4) with a daily dose of 500 mg given as twice daily dosing (250 mg twice daily). Increase the daily dose every 2 weeks by increments of 500 mg to a maximum recommended daily dose of 1500 mg (750 mg twice daily).

(b) (4)

BACKGROUND

The Applicant has submitted an NDA for SPRITAM under 505(b)(2) using KEPPRA[®] (levetiracetam) immediate release tablets as the reference listed drug. In the agreed Pediatric Study Plan, it was agreed that for pediatric sub-populations that are labeled but for which weight-based dosing is recommended, a pediatric waiver would be requested under the grounds that the product does not represent a meaningful benefit over existing therapies (i.e., Keppra Oral Solution) and the product is unlikely to be used in a substantial number of pediatric patients. The practical implication of this agreement is that the SPRITAM label would not include any of the mg/kg dosing that is in the KEPPRA[®] label. At the time, it was thought that this would include dosing recommendations for primary generalized tonic-clonic (PGTC) seizures in pediatric patients ages 6 to < 16 years. However, during labeling negotiations, the Applicant proposed tablet dosing in this population which caused a reevaluation of the previous agreement.

LABELING REVIEW

There are two key sections of the KEPPRA[®] label that were considered during this review. The first is the dosing recommendations for PGTC in pediatric patients ages 6 to < 16 years as reproduced below:

2.4 Dosing for Primary Generalized Tonic-Clonic Seizures

Pediatric Patients Ages 6 to < 16 Years

Initiate treatment with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg twice daily). The effectiveness of doses lower than 60 mg/kg/day has not been adequately studied. Patients with body weight \leq 20 kg should be dosed with oral solution. Patients with body weight above 20 kg can be dosed with either tablets or oral solution [see Dosage and Administration (2.1)]. Only whole tablets should be administered.

From this text, it is clear that the label provides for the use of tablets in pediatric patients > 20 kg which is consistent with their use in the study that supported approval. The label, however, does not explicitly state which doses should be used. Since SPRITAM only comes in tablets, the question then arises as to which specific doses should be recommended for this population. It would not be sufficient to just remove any reference to mg/kg dosing (i.e., the first three sentences in the text above) and retain the rest of the text because the prescriber would have no idea what doses are approved in this population.

One might take a strict interpretation of the KEPPRA[®] label to infer that dosing with the tablet is only acceptable when the calculated mg/kg dose for an individual patient happens to be equal to one of the strength available. This would be impracticable, however, as only patients weighing exactly 25 kg or 50 kg would be able to receive the tablet. And once the patient gained an extra kg, they would have to revert to solution dosing.

Another interpretation of the KEPPRA[®] label would be to use dosing information in pediatric patients with partial onset seizures (POS) to infer the intended tablet dosing in PGTC patients. This is the approach the Applicant proposed. The key section of the KEPPRA[®] label is reproduced below:

2.4 Dosing for Partial Onset Seizures

Pediatric Patients

4 Years to < 16 Years

Initiate treatment with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg twice daily). Increase the daily dose every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg twice daily). If a patient cannot tolerate a daily dose of 60 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 44 mg/kg. The maximum daily dose was 3000 mg/day.

For KEPPRA tablet dosing in pediatric patients weighing 20 to 40 kg, initiate treatment with a daily dose of 500 mg given as twice daily dosing (250 mg twice daily). Increase the daily dose every 2 weeks by increments of 500 mg to a maximum recommended daily dose of 1500 mg (750 mg twice daily).

For KEPPRA tablet dosing in pediatric patients weighing more than 40 kg, initiate treatment with a daily dose of 1000 mg/day given as twice daily dosing (500 mg twice daily). Increase the daily dose every 2 weeks by increments of 1000 mg/day to a maximum recommended daily dose of 3000 mg (1500 mg twice daily).

Note that the mg/kg dosing for pediatric patients with POS is identical to the dosing for pediatric patients with PGTC. This section of the label, however, also includes explicit instructions for tablet dosing in the second and third paragraphs. These tablet doses are presumably intended to be acceptable approximations of the mg/kg dosing described in the first paragraph. Since dosing for POS and PGTC is identical, one would come to the logical conclusion that the tablet dosing instructions for POS would also apply to PGTC. Additionally, both the body weight based and fixed dosing regimens were evaluated in clinical trials to support approval of KEPPRA® for POS and PGTC. Based on this reasoning, we agree with the Applicant that the dosing regimens described in the second and third paragraphs of the text above should be applied to Section 2.4 of the SPRITAM label to provide tablet dosing for primary generalized tonic-clonic seizures in pediatric patients ages 6 to ^{(b) (4)} years.

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/s/

KEVIN M KRUDYS
07/22/2015

BEI YU
07/22/2015

YUXIN MEN
07/22/2015

Clinical Pharmacology Review

NDA#	207958
Date of Original submission:	10/1/14
Brand Name:	Spritam
Generic Name:	Levetiracetam (b) (4)
Administration Route:	Oral
Strength and Formulation:	(b) (4) (Tablet): 250, 500, 750, and 1000 mg
Sponsor:	Aprecia Pharm.
Indication:	Partial Onset Seizures; Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy; Primary Generalized Tonic-Clonic Seizures
Submission Type:	Standard
OCP Review Team:	Bei Yu, Ph.D., Angela Men, M.D., Ph.D., Kevin Krudys, Ph.D.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY	2
1.1 RECOMMENDATION	2
1.2 PHASE IV COMMITMENT/REQUIREMNT	2
1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY	2
2 QUESTION BASED REVIEW (QBR)	4
2.1 SPECIFIC QUESTIONS	4
3. DETAILED LABELING RECOMMENDATION	7

APPENDIX: INDIVIDUAL STUDY REVIEW

1. EXECUTIVE SUMMARY

The sponsor submitted the NDA under 505 (b)(2) for Spritam™ levetiracetam (b)(4) using KEPPRA® (levetiracetam) immediate release (IR) tablets as the reference listed drug (RLD). Spritam® (levetiracetam (b)(4)) was considered to be a high-dose solid oral dosage form product in a (b)(4) presentation that aids in patient compliance and ease of dosing for those who have difficulty swallowing large traditional tablets or capsules. The (b)(4) designed through a process called three-dimensional printing (3DP), dispersed very rapidly in the mouth when taken with a sip of liquid, which then made it very easy to swallow.

In this submission, the sponsor submitted two studies to support its approval for Spritam: a BA/BE study (Study LVA-P3-439/CL-LEV-001-R001) bridging the test drug and the RLD, and a PK study (Study CL-LEV-003/ Novum 11369701) evaluating levetiracetam PK following administration of Spritam without taking water. No efficacy trial was conducted.

1.1 RECOMMENDATION

The NDA submission is acceptable from a Clinical Pharmacology perspective and the OCP recommends approval for NDA 207958 pending satisfactory agreement with the sponsor on the label.

1.2 PHASE IV COMMITMENT/REQUIREMNT

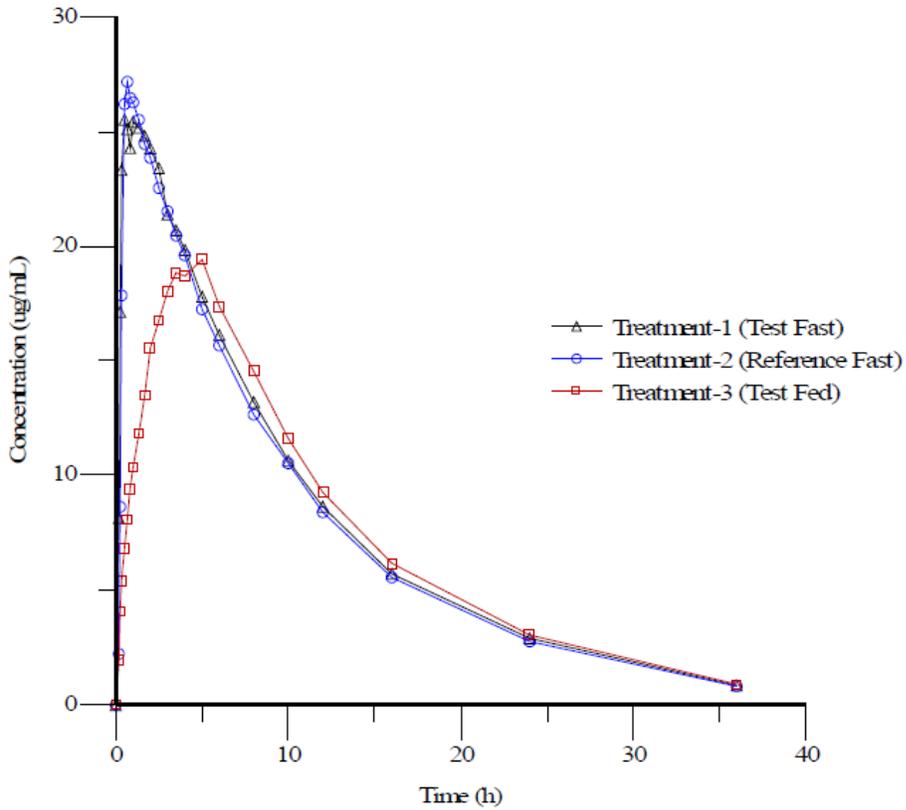
None.

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY

Following Spritam administration at 1000 mg in fasted subjects, absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour. Spritam was shown to have equivalent rate and extent of absorption to Keppra® IR tablets under fasted conditions. High fat food has no effect on the extent of drug absorption (AUC) for Spritam. However, food delays the drug absorption by 3.4 hours (from 0.6 to 4 hours) and decreases C_{max} by 36% for Spritam, which is unlikely to be clinically significant.

Spritam should be taken with a sip of (b)(4).

Mean plasma concentration versus time profiles of levetiracetam following administration of Spritam and Keppra IR at 1000 mg under fasted conditions, and Spritam at 1000 mg under fed conditions are shown below:



Signatures

Bei Yu (CP primary reviewer)

Angela Men (CP TL)

Division of Clinical Pharmacology 1

Kevin Krudys (PM reviewer)

2 QUESTION BASED REVIEW (QBR)

2.1 Specific Questions

2.1.1 Are PK profiles of levetiracetam comparable between Spritam and Keppra IR (RLD)?

Yes. A 3-way crossover BA/BE study (LVA-P3-439/CL-LEV-001-R001) was conducted to compare PK profiles of levetiracetam between single dose of Spritam and Keppra IR at 1000 mg under fasted conditions; in addition, food effect of 1000 mg of Spritam was evaluated in the study.

The study results indicated that PK profiles of levetiracetam are comparable between Spritam and Keppra IR with acceptance range of 90% CI for ratios of two treatments of geometric least squares means for C_{max} and AUC falling into BE criteria, 80-125%.

High fat food has no effect on the extent of drug absorption (AUC) for Spritam. However, food delays the drug absorption by 3.4 hours (from 0.6 to 4 hours) and decreases C_{max} by 36% for Spritam.

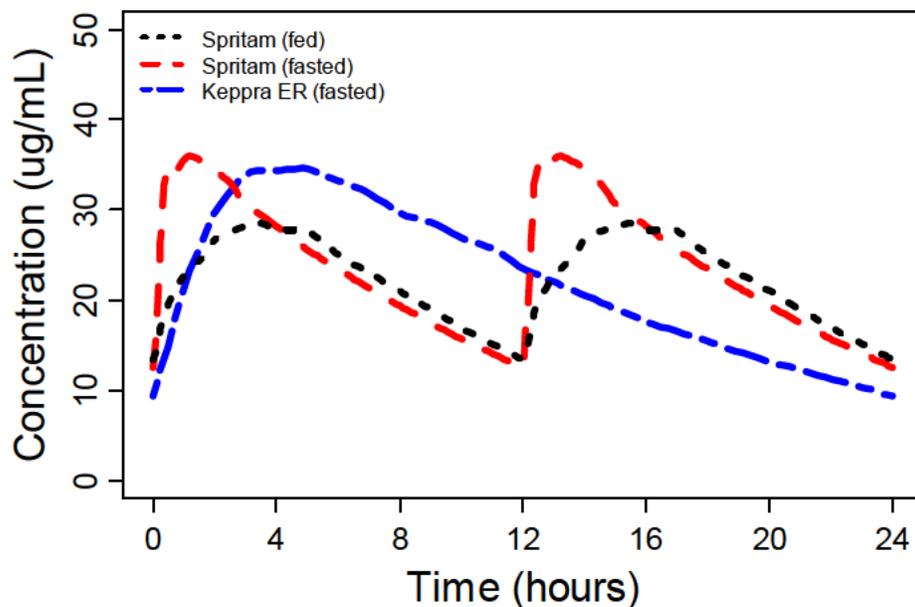
2.1.2 Will administration of Spritam with food result in decreased efficacy?

No, it is unlikely that the reduction in C_{max} due to food effect will decrease efficacy because the extent of drug absorption (AUC) has no change and the therapeutic concentrations of levetiracetam fall into the concentration ranges of the approved Keppra IR and ER throughout the dosing interval.

Study LVA-P3-439/CL-LEV-001-R001 showed that food delays drug absorption by 3.4 hours and decreases C_{max} by 36%, although AUC was comparable. Simulations using nonparametric superposition were performed to explore steady-state exposures for three different dosing regimens: Spritam 1000 mg bid (fasted), Spritam 1000 mg bid (fed) and extended release levetiracetam 2000 mg qd (fasted). The results are displayed in Figure 1. The food effect at steady-state is predicted to be slightly lower than that after a single dose (31% vs. 36%). A few observations from the simulation results provide reassurance that effective plasma concentrations will be maintained when Spritam is administered with food:

- The shape of the plasma concentration-time curves is similar in the fed and fasted states. The only difference is the delayed T_{max} and lower C_{max}. The trough concentration is comparable for the two regimens and levetiracetam concentrations in the fed state do not venture outside the range of concentrations observed in the fasted state or after administration of extended release levetiracetam.
- Over a substantial portion of the day (~13 to 24 hours in Figure 1), levetiracetam concentrations in the fed state are actually higher than the concentrations for a regimen that has established efficacy (extended release levetiracetam).

Figure 1: Twenty-Four Hour Steady State Profiled for Spritam 1000 mg bid (fed), Spritam 1000 mg bid (fasted) and Extended Release Keppra 2000 mg qd (fasted)

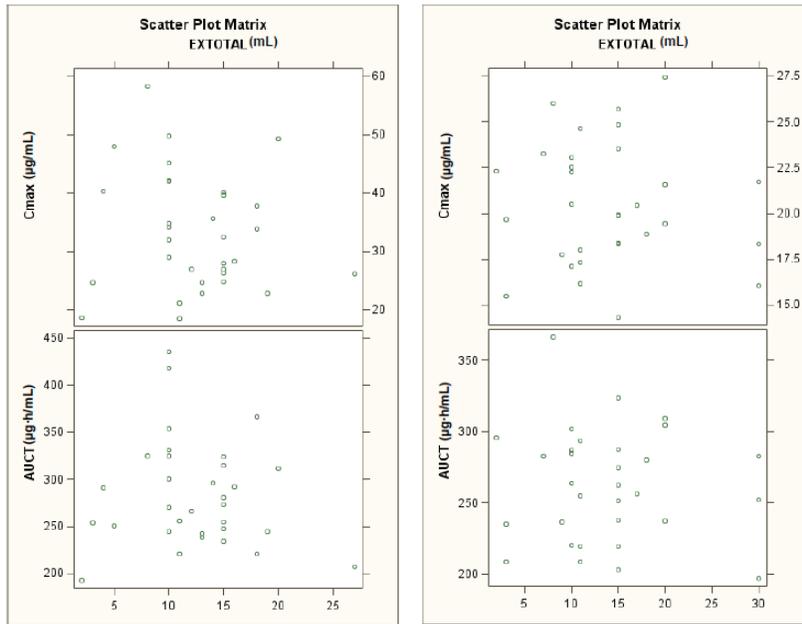


Furthermore, it is not unreasonable to think that if the Sponsor conducted a BA/BE study between Spritam and Keppra IR in the fed state, the results would have shown bioequivalence. Studies with Keppra IR have shown that food reduces C_{max} by 20% in one study and 28% in another (Ref: OCP review for NDA 21035). The magnitude of the food effect for Spritam (36%) was only moderately larger compared to these studies.

2.1.3 Does volume of water a matter for Spritam administration to support the label in “sip of (b) (4)”?

No. In the BA/BE study (LVA-P3-439/CL-LEV-001-R001), the sponsor assessed the correlation between the volume of water consumed by subjects during drug administration (ranged from 2 mL to 30 mL) and levetiracetam systemic exposures (AUC and C_{max}). No clear trend or correlation could be observed between the amount of water ingested with Spritam and the PK parameters (Figure showed below). Additionally, no subject needed additional water after the initial sip and thus a sip of water is sufficient for the drug administration.

Figure 2: Correlations between systemic exposures (AUC and Cmax) of levetiracetam and the amount of water taken with Spritam at 1000 mg under fasted (Left panel) and fed conditions (right panel).



Furthermore, the sponsor evaluated levetiracetam PK following single dose of Spritam at 1000 mg without taking water under fasted conditions in 12 healthy volunteers (Study CL-LEV-003/Novum 11369701). Eleven out of 12 test dosing units disintegrated and were swallowed in 12 min; 1 out of 12 (Subject #8) had a prolonged disintegration of Spritam of ~28 min with prolonged Tmax of 2.5 h. Levetiracetam PK parameters are comparable to those in the BA/BE study (LVA-P3-439/CL-LEV-001-R001) except for a prolonged Tmax following Spritam administration without taking water:

Mean (CV)	With sip of water (n=32)	Without taking water (n=12)
Cmax (ug/mL)	33.3 (30.1)	31.4 (22)
AUCt (ug.h/mL)	283.7 (20)	287.1 (18.9)
Tmax (hr, median)	0.58	0.92

3. DETAILED LABELING RECOMMENDATION

12.3 Pharmacokinetics

Absorption and Distribution

(b) (4) Peak plasma concentrations of levetiracetam occurred in about an hour following oral administration in fasted subjects. In a crossover study in healthy volunteers, SPRITAM was shown to have equivalent rate and extent of absorption to (b) (4) levetiracetam IR tablets under fasting conditions (b) (4) high fat meal (b) (4) does not affect the extent of absorption of SPRITAM but it decreases C_{max} by (b) (4) 36% and delays t_{max} by (b) (4) 3.4 hours. (b) (4)

(b) (4)

The oral bioavailability of levetiracetam tablets is (b) (4) % and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of levetiracetam but it decreases C_{max} by 20% and delays t_{max} by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500-5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

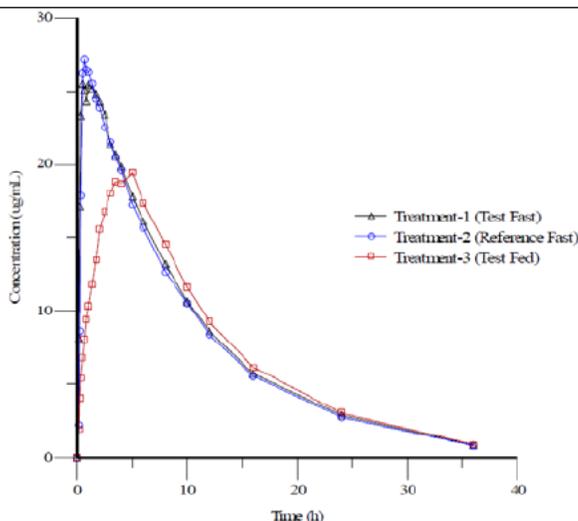
APPENDIX: INDIVIDUAL STUDY REVIEW

BABE study

Study LVA-P3-491/or CL-LEV-001-R00	Single Dose Crossover Comparative Bioavailability Study Under Fasting Conditions and Food Effect Study of Levetiracetam (b) (4) 1000 mg Compared to 1000 mg Keppra® Film-Coated Tablets in Healthy Male and Female Volunteers.
Principle Investigator	Eric Sicard, M.D. Algorithme Pharma Inc.
Study Site	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1
Study Period	10/9/13 – 10/25/13
Study Objectives	<p>1) to determine and compare the levetiracetam plasma concentrations following single administration of levetiracetam (b) (4) 1000 mg and film-coated Keppra® tablet 1000 mg in normal healthy volunteers, and to evaluate the effect of food consumption on the PK profile of levetiracetam (b) (4) 1000 mg;</p> <p>2) to determine the safety and tolerability of levetiracetam (b) (4) 1000 mg compared to Keppra® film-coated 1000 mg tablets in healthy volunteers.</p>
Study Design and Dose Administration	<p>The study was a single center, randomized, single dose, laboratory-blinded, 3-period, 3-sequence, crossover design in healthy male and female subjects. The following investigational products were to be administered:</p> <p>Test: 1 x Levetiracetam 1000 mg (b) (4)</p> <p>Reference: 1 x Keppra® 1000 mg film-coated tablet</p> <p>A single oral dose of the assigned levetiracetam treatment was administered in each study period according to the randomization as follows:</p> <p>Treatment-1 (Test Fast): One Levetiracetam 1000 mg (b) (4) under fasting conditions; After a supervised overnight fast, a single dose of the levetiracetam (b) (4) formulation was to be orally administered in the morning. The (b) (4) was to be placed on each subject's tongue followed by a sip of water from a glass containing 30 mL of water.</p> <p>Treatment-2 (Reference Fast): One Keppra® 1000 mg film-coated tablet under fasting conditions; After a supervised overnight fast, a single dose of the film-coated tablet of levetiracetam (Keppra®) was to be orally administered in the morning with approximately 240 mL of water at ambient temperature.</p> <p>Treatment-3 (Test Fed): One Levetiracetam 1000 mg (b) (4) under fed conditions; After a supervised overnight fast, subjects were to receive a standardized high fat, high-calorie meal 30 minutes before drug administration. Thirty minutes after the start of breakfast, a single dose of the levetiracetam (b) (4) formulation was to be orally</p>

	<p>administered in the morning. The (b) (4) was to be placed on each subject's tongue followed by a sip of water from a glass containing 30 mL of water.</p> <p>The amount of water consumed for levetiracetam 1000 mg (b) (4) was measured for each subject in Treatments 1 and 3, and is shown in the table below:</p> <p>Table 4. Total Volume of Water Consumed by Subjects (mL)</p> <table border="1" data-bbox="560 506 1317 793"> <thead> <tr> <th></th> <th>Treatment-1 (N=32)</th> <th>Treatment-3 (N=32)</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>32</td> <td>32</td> </tr> <tr> <td>Mean (SD)</td> <td>12 (5)</td> <td>14 (7)</td> </tr> <tr> <td>Median</td> <td>12.5</td> <td>13.0</td> </tr> <tr> <td>Min, Max</td> <td>2, 27</td> <td>2, 30</td> </tr> </tbody> </table> <p><i>Reviewer's comments: no additional water was provided during the study for Treatments 1 and 3.</i></p> <p>The products were to be administered to 33 healthy male and female subjects according to the Table below:</p> <table border="1" data-bbox="513 989 1385 1171"> <thead> <tr> <th></th> <th>Period 1</th> <th>Period 2</th> <th>Period 3</th> </tr> </thead> <tbody> <tr> <td>Sequence 1 (n= 11)</td> <td>Treatment-1</td> <td>Treatment-2</td> <td>Treatment-3</td> </tr> <tr> <td>Sequence 2 (n= 11)</td> <td>Treatment-2</td> <td>Treatment-3</td> <td>Treatment-1</td> </tr> <tr> <td>Sequence 3 (n= 11)</td> <td>Treatment-3</td> <td>Treatment-1</td> <td>Treatment-2</td> </tr> </tbody> </table> <p>The drug administrations were separated by a wash-out of 7 days.</p>		Treatment-1 (N=32)	Treatment-3 (N=32)	N	32	32	Mean (SD)	12 (5)	14 (7)	Median	12.5	13.0	Min, Max	2, 27	2, 30		Period 1	Period 2	Period 3	Sequence 1 (n= 11)	Treatment-1	Treatment-2	Treatment-3	Sequence 2 (n= 11)	Treatment-2	Treatment-3	Treatment-1	Sequence 3 (n= 11)	Treatment-3	Treatment-1	Treatment-2
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Study Population	<p>33 subjects were enrolled, and 32 subjects completed the study. One subject (# 017) was withdrawn due to a positive cannabinoids (THC50) test.</p> <p><u>Age:</u> 18-48 (30) years</p> <p><u>Gender:</u> 19 M/14 F</p> <p><u>Race:</u> 27 Caucasian, 4 Black, 1 Asian, and 1 other.</p>																															
Investigational Product	<table border="1" data-bbox="508 1444 1388 1759"> <thead> <tr> <th>Drug Code:</th> <th>Test</th> <th>Reference</th> </tr> </thead> <tbody> <tr> <td>Formulation:</td> <td>Levetiracetam 1000 mg (b) (4)</td> <td>Keppra® 1000 mg film-coated tablet</td> </tr> <tr> <td>Manufacturer:</td> <td>Aprecia Pharmaceuticals, USA</td> <td>UCB Inc., USA</td> </tr> <tr> <td>Batch No.:</td> <td>LV-13-001</td> <td>93349</td> </tr> <tr> <td>Manufacturing Date:</td> <td>06Sep2013</td> <td>N/AV</td> </tr> <tr> <td>Expiry Date:</td> <td>(b) (4) Retest date)</td> <td>(b) (4)</td> </tr> <tr> <td>Measured Content:</td> <td>(b) (4) % of label claim</td> <td>(b) (4) % of label claim</td> </tr> </tbody> </table>	Drug Code:	Test	Reference	Formulation:	Levetiracetam 1000 mg (b) (4)	Keppra® 1000 mg film-coated tablet	Manufacturer:	Aprecia Pharmaceuticals, USA	UCB Inc., USA	Batch No.:	LV-13-001	93349	Manufacturing Date:	06Sep2013	N/AV	Expiry Date:	(b) (4) Retest date)	(b) (4)	Measured Content:	(b) (4) % of label claim	(b) (4) % of label claim										
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Measured Content:	(b) (4) % of label claim	(b) (4) % of label claim																														
Sampling: Blood	<p>Blood samples were collected prior to and 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours after drug administration.</p>																															
Urine	<p>none</p>																															

Feces	none																
Analysis	<p>The experimental samples were assayed for levetiracetam at the analytical facility of (b) (4) using a validated HPLC method with MS/MS detection:</p> <p>(b) (4)</p> <p>The subject sample analysis was performed between (b) (4) and (b) (4), including re-assays and incurred samples.</p> <table border="1"> <thead> <tr> <th></th> <th>Levetiracetam</th> </tr> </thead> <tbody> <tr> <td>Matrix</td> <td>Plasma</td> </tr> <tr> <td>Method</td> <td>LC/MS/MS</td> </tr> <tr> <td>Linear Range (µg/ml)</td> <td>0.25-65.0</td> </tr> <tr> <td>LLOQ (µg/mL)</td> <td>0.25</td> </tr> <tr> <td>QCs</td> <td>0.25, 0.75, 9, 50 µg/mL</td> </tr> <tr> <td>Inter-run precision</td> <td>2.1 - 6.6%</td> </tr> <tr> <td>Inter-run accuracy</td> <td>95.3 – 105.1 %</td> </tr> </tbody> </table> <p>Quality control assay validation is acceptable.</p>		Levetiracetam	Matrix	Plasma	Method	LC/MS/MS	Linear Range (µg/ml)	0.25-65.0	LLOQ (µg/mL)	0.25	QCs	0.25, 0.75, 9, 50 µg/mL	Inter-run precision	2.1 - 6.6%	Inter-run accuracy	95.3 – 105.1 %
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PK Assessment	<p>The PK parameters of interest for this study were to be C_{max}, AUC_{0-T} and AUC_{0-∞}. Other parameters including T_{max}, AUC_{0-T/∞}, K_{el} and T_{1/2el} were to be calculated and provided for information purposes only.</p> <p>Statistical analysis of other PK parameters based on a parametric ANOVA model. Two-sided 90% confidence interval of the ratio of geometric LS means obtained from the ln-transformed PK parameters.</p>																
Safety Assessment	Vital signs, orthostatic vital signs, ECG, Clinical laboratory, and AEs.																
PD Assessment	none																
Pharmacokinetic Results	The mean plasma concentration versus time profiles on linear scales for levetiracetam is presented below:																



PK Comparison between treatments of Keppra and Levetiracetam (b) (4) at 1000 mg under fasted conditions:

Table 9. Summary of Main Study Results – Levetiracetam - Treatment-1 vs Treatment-2

PARAMETER	TREATMENT-1 (Test Fast)		TREATMENT-2 (Reference Fast)	
	MEAN	C.V.	MEAN	C.V.
C_{max} (µg/mL)	33.273	30.1	30.480	19.0
$\ln(C_{max})$	3.4616	8.6	3.3991	5.7
T_{max} (hours) *	0.58	73.7	0.58	69.9
AUC_{0-T} (µg·h/mL)	283.689	20.0	274.934	18.2
$\ln(AUC_{0-T})$	5.6298	3.4	5.6012	3.2
$AUC_{0-\infty}$ (µg·h/mL)	292.927	19.9	284.300	18.0
$\ln(AUC_{0-\infty})$	5.6619	3.4	5.6349	3.1
$AUC_{0-T/\infty}$ (%)	96.84	1.4	96.70	1.7
λ_z (hours ⁻¹)	0.0990	13.7	0.0995	16.1
T_{half} (hours)	7.13	13.3	7.14	16.3

* median is presented

Table 10. Comparison of Results with Standards for Relative Bioavailability – Levetiracetam - Treatment-1 vs Treatment-2

PARAMETER	Intra-CV	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
		TREATMENT-1 (Test Fast)	TREATMENT-2 (Reference Fast)		LOWER	UPPER
C_{max}	15.7	31.924	29.988	106.45	99.74	113.62
AUC_{0-T}	4.7	279.151	271.174	102.94	100.93	105.00
$AUC_{0-\infty}$	4.9	288.300	280.489	102.78	100.72	104.89

* units are µg/mL for C_{max} and µg·h/mL for AUC_{0-T} and $AUC_{0-\infty}$

Reviewer's comments: PK profiles of levetiracetam are BE between treatments of Keppra IR and Levetiracetam (b) (4) at 1000 mg under fasted conditions.

Food effect of levetiracetam ^{(b) (4)} at 1000 mg:
Table 11. Summary of Main Study Results – Levetiracetam - Treatment-3 vs Treatment-1

PARAMETER	TREATMENT-3 (Test Fed)		TREATMENT-1 (Test Fast)	
	MEAN	C.V.	MEAN	C.V.
C _{max} (µg/mL)	20.481	16.3	33.273	30.1
ln (C _{max})	3.0066	5.5	3.4616	8.6
T _{max} (hours) *	4.00	21.6	0.58	73.7
AUC _{0-T} (µg·h/mL)	262.550	15.1	283.689	20.0
ln (AUC _{0-T})	5.5595	2.7	5.6298	3.4
AUC _{0-∞} (µg·h/mL)	272.565	15.2	292.927	19.9
ln (AUC _{0-∞})	5.5968	2.7	5.6619	3.4
AUC _{0-T/∞} (%)	96.35	1.8	96.84	1.4
λ _Z (hours ⁻¹)	0.0985	14.9	0.0990	13.7
T _{half} (hours)	7.19	15.3	7.13	13.3

* median is presented

Table 12. Comparison of Results with Standards for Relative Bioavailability – Levetiracetam- Treatment-3 vs Treatment-1

PARAMETER	Intra-CV	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
		TREATMENT-3 (Test Fed)	TREATMENT-1 (Test Fast)		LOWER	UPPER
C _{max}	15.7	20.384	31.924	63.85	59.79	68.19
AUC _{0-T}	4.7	263.660	279.151	94.45	92.58	96.36
AUC _{0-∞}	4.9	273.675	288.300	94.93	93.00	96.89

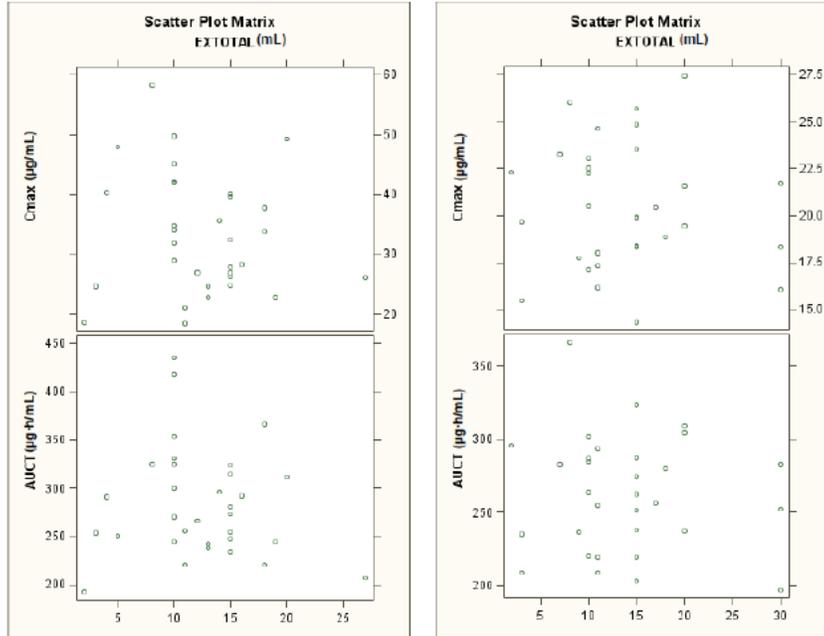
* units are µg/mL for C_{max} and µg·h/mL for AUC_{0-T} and AUC_{0-∞}

Reviewer's comments: food delays drug absorption by 3.4 hours (from 0.6 hr to 4 hr), and decreases C_{max} by 36%. There is no food effect on AUC. The clinical impact of the C_{max} decrease by the food was further assessed by PM reviewer, Dr. Kevin Krudys (Refer to Specific Question 2).

Effect of water intake:

The volume of water consumed by subjects during drug administration ranged from 2 mL to 30 mL. No subject asked for additional water to be provided. No clear trend or correlation could be observed between the amount of water ingested with the Test product and the measured plasma concentrations nor the PK parameters. No subject needed additional water after the initial sip and thus a sip of water is sufficient to administer this rather large size

dosage unit without the need for a full glass of water. Furthermore, following statistical analysis, no significant correlation was observed between the volume of water consumed by subjects receiving Treatment-1 or -3 and the C_{max} or AUC_{0-T} in either fasted or fed conditions.



Reviewer's comments: No clear trend or correlation could be observed between the amount of water (2-30 mL) ingested with the Spritam and PK parameters (C_{max} and AUC) under fasted (left panel) and fed (right panel) conditions.

Safety

There was no SAE or death in the study. No subject was withdrawn from the study for safety reasons.

Treatments	Adverse Events				
	Severity			Causality	
	Mild	Moderate	Severe	Reasonable Possibility	No Reasonable Possibility
Treatment-1 (Test Fast)	32	7	0	33	6
Treatment-2 (Reference Fast)	31	4	0	28	7
Treatment-3 (Test Fed)	16	4	0	13	7
Total number of adverse events	79	15	0	74	20

Conclusion

PK profiles of levetiracetam are comparable between treatments of Spritam and Keppra IR at 1000 mg under fasted conditions. For Spritam, food delays drug absorption by 3.4 hours (from 0.6 hr to 4 hr), and decreases C_{max} by 36%; There is no food effect on AUC.

Reviewer's comments: Biopharmaceutical inspection for clinical site and analytical site of the study was request. The Division of Bioequivalence and GLP Compliance (DBGLPC) recommends accepting data without an on-site inspection because Office of Scientific Investigations inspected the sites within the last four year.

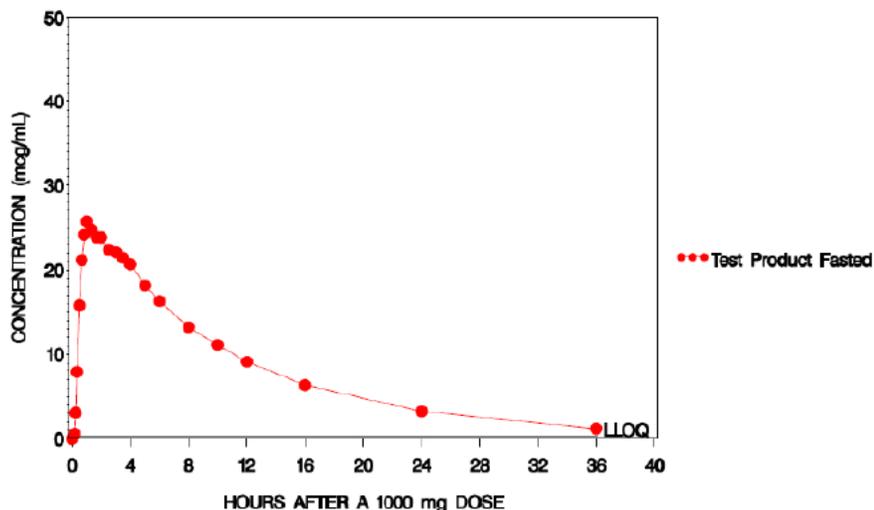
PK study in healthy subjects:

<p>Study CL-LEV-003/or Novum 11369701</p>	<p>A Study to Characterize the Pharmacokinetics of a Test Formulation of Levetiracetam (b) (4) 1000 mg (Aprecia Pharmaceuticals Company) in Healthy Male and Female Volunteers under Fasted Conditions.</p>						
<p>Principle Investigator</p>	<p>Carmelo V. Rillera, M.D.</p>						
<p>Study Site</p>	<p>Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121 United States of America (USA)</p>						
<p>Study Period</p>	<p>12/28/13 – 12/29/13</p>						
<p>Study Objectives</p>	<p>To characterize the PK of a test formulation of levetiracetam (b) (4) 1000 mg (Aprecia Pharmaceuticals) following single-dose oral administration without water in the fasted state in healthy adult male and female subjects.</p>						
<p>Study Design and Dose Administration</p>	<p>This was a single-dose, one-treatment, one-period, open-label study under fasted conditions. The study was conducted with 12 healthy adult subjects.</p> <p>At dosing time, a clinical staff member placed the study drug on top of the subject’s tongue. The subject was instructed to close their mouth and let the dosing unit disintegrate on their tongue, without sucking, chewing or biting or other unusual tongue movements. Once the dosing unit was disintegrated, subjects were instructed to swallow the medication. No water was provided during the drug administration procedure. However, water may have been provided for safety reasons after dosing if a subject had difficulty swallowing the study drug. The amount of water ingested and the time of ingestion was recorded. The dissolution times are tabulated below:</p> <table border="1" data-bbox="503 1228 901 1627"> <thead> <tr> <th colspan="2">Period I</th> </tr> <tr> <th>Subject</th> <th>Time to Dissolution</th> </tr> </thead> <tbody> <tr> <td colspan="2" style="text-align: right;">(b) (4)</td> </tr> </tbody> </table> <p>(b) (4) of the 12 (b) (4) test dosing units disintegrated and were swallowed within (b) (4) minutes of placement on the top of the subject’s tongue, with (b) (4) of the 12 (b) (4) test dosing units dissolving within (b) (4) minutes of administration. (b) (4) had a prolonged disintegration of the (b) (4) of about (b) (4) minutes.</p>	Period I		Subject	Time to Dissolution	(b) (4)	
Period I							
Subject	Time to Dissolution						
(b) (4)							
<p>Study Population</p>	<p>12 subjects were enrolled, and completed the study.</p>						

	<u>Age:</u> 21-45 (34) years <u>Gender:</u> 6 M/6 F <u>Race:</u> 1 Caucasian, 7 Black, and 4 other.																
Investigational Product	Levetiracetam (b) (4) 1000 mg Aprecia Pharmaceuticals Lot No.: LV-13-001 Re-test Date: (b) (4)																
Sampling: Blood	Blood samples were collected before dosing and 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours after drug administration for analysis of plasma levetiracetam concentrations. (Subject 11 had a missing sample at 36 h post dose)																
Urine	none																
Feces	none																
Analysis	<p>The experimental samples were assayed for levetiracetam at the analytical facility of (b) (4) using a validated HPLC method with MS/MS detection:</p> <p>(b) (4)</p> <p>The subject sample analysis was performed between (b) (4) and (b) (4), including re-assays and incurred samples.</p> <table border="1"> <thead> <tr> <th></th> <th>Levetiracetam</th> </tr> </thead> <tbody> <tr> <td>Matrix</td> <td>Plasma</td> </tr> <tr> <td>Method</td> <td>LC/MS/MS</td> </tr> <tr> <td>Linear Range (µg/ml)</td> <td>0.25-65.0</td> </tr> <tr> <td>LLOQ (µg/mL)</td> <td>0.25</td> </tr> <tr> <td>QCs</td> <td>0.25, 0.75, 9, 50 µg/mL</td> </tr> <tr> <td>Inter-run precision</td> <td>2.1 - 6.6%</td> </tr> <tr> <td>Inter-run accuracy</td> <td>95.3 – 105.1 %</td> </tr> </tbody> </table> <p>Quality control assay validation is acceptable.</p>		Levetiracetam	Matrix	Plasma	Method	LC/MS/MS	Linear Range (µg/ml)	0.25-65.0	LLOQ (µg/mL)	0.25	QCs	0.25, 0.75, 9, 50 µg/mL	Inter-run precision	2.1 - 6.6%	Inter-run accuracy	95.3 – 105.1 %
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PK Assessment	AUC _{0-t} , AUC _{0-inf} , C _{max} , T _{max} , K _{el} and T _½ .																
Safety Assessment	Vital signs, orthostatic vital signs, ECG, Clinical laboratory, and AEs.																
PD Assessment	none																
Pharmacokinetic Results	The mean plasma concentration versus time profiles on linear scales for levetiracetam is presented below:																

LEVETIRACETAM STUDY NO. 11369701

MEAN PLASMA CONCENTRATIONS (N=12)



Mean concentration values below LLOQ in the terminal phase are not plotted
LLOQ = 0.250 mcg/mL

PK parameters of levetiracetam after treatment of Spritam at 1000 mg under fasted conditions:

Table 2.1 Summary of Pharmacokinetic Parameters of Untransformed Data: Levetiracetam (N = 12)

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)	Geometric mean (%CV)
	Test A (N = 12 datasets)	Test A (N = 12 datasets)
AUC _{0-t} (mcg·hr/mL)	287.1213 ± 54.1823 (18.8709)	282.7220 (18.2898)
AUC _{0-inf} (mcg·hr/mL)	302.8005 ± 56.4209 (18.6330)	298.2726 (18.0557)
AUC _{0-t} /AUC _{0-inf} ratio	0.9481 ± 0.0234 (2.4692)	N/A
C _{max} (mcg/mL)	31.4112 ± 6.9215 (22.0350)	30.7608 (21.3077)
T _{max} (hr)	0.9850 ± 0.5436 (55.1894)	N/A
Median T _{max} (hr) (min – max)	0.92 (0.33 – 2.50)	N/A
K _{e1} (1/hr)	0.0858 ± 0.0105 (12.2553)	N/A
T _{1/2} (hr)	8.1928 ± 1.0369 (12.6564)	N/A

Reviewer's comments: Systemic exposures (C_{max} and AUC) of levetiracetam for Subject 8 are comparable to those of other subjects, but T_{max} was prolonged to 2.5 hours. At a worst case scenario, e.g., patients take Spritam with high fat food without taking water, the drug absorption will be delayed as long as 5-6 hours. Thus, Spritam should be taken with a sip of (b) (4).

Safety

There was no SAE or death in the study. No subject was withdrawn from the study for safety reasons. No adverse events were localized to the dosing site.

Conclusion

The PK of levetiracetam (b) (4) 1000 mg (Aprecia Pharmaceuticals) in this study (no water provided during drug administration procedure) are similar to those from a previous single-

dose clinical trial conducted with the test ^{(b) (4)} product administered with water under fasted conditions (Sponsor Protocol LVA-P3-491), though the median T_{max} tended to be longer in this study (0.92 versus 0.58 hours).

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/s/

BEI YU
06/05/2015

KEVIN M KRUDYS
06/05/2015

YUXIN MEN
06/05/2015