CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207958Orig1s000

MEDICAL REVIEW(S)

Clinical Team Leader Review

Date	July 23, 2015
Subject	Clinical Team Leader Review
NDA/BLA # Supplement#	207958
Applicant	Aprecia Pharmaceuticals
Date of Submission	October 1, 2014
PDUFA Goal Date	August 1, 2015
Proprietary Name / Non-Proprietary Name	Levetiracetam/ Spritam
Dosage form(s) / Strength(s)	Tablets: 250 mg, 500 mg, 750 mg and 1000 mg
Applicant Proposed Indication(s)/Population(s)	1. Partial Onset Seizures: 4 years of age and older weighing ≥20 kg) 2. Juvenile Myoclonic Epilepsy: 12 years of age and older 3. Primary Generalized Tonic-clonic Seizures: 6 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as the proposed indication.

1. Introduction and Background

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.

SPRITAM is a formulation of levetiracetam that utilizes a new manufacturing process, three-dimensional printing (3DP) technology, which allows for the drug to rapidly disperse in the mouth when taken with a sip of (b) (4). The Sponsor believes that this makes their formulation easily swallowed.

The present application is a 505(b)(2) submission that relies on the reference labeled drug product (RLD), Keppra, and pharmacokinetic bridging studies comparing this product to the RLD. The sponsor has provided a package insert that includes labeling for the same indications, similar patient populations (including pediatric patients), and dosing as that of the RLD, Keppra. It is noteworthy that an agreed upon iPSP[1] acknowledged that "for pediatric sub-populations that are labeled in pediatrics, but for which weight based dosing is recommended, i.e., pediatric patients with partial complex seizures under age 4 years and primary generalized tonic-clonic seizures (b) (4)" a waiver will be requested under the grounds that the product does not represent a meaningful benefit over existing therapies and the product is unlikely to be used in a substantial number of pediatric patients as these patients can use the existing oral solution.

2. Product Quality

This review was performed by a number of the staff from OTR, ONDP, OPF, OPPQ and OPRO, including M. Khan, M. Heimann, A Khairuzzaman, V. Shah, M. Kakhi, Z. Rahman, A, Ponta and T. Bouie.

Approval is recommended.

The review noted that the product is novel as it quickly disintegrates in the mouth and is prepared by a 3D printing process. Unlike orally disintegrating tablets which are usually meant for low dose drugs, the present technology can be used for higher doses. The review noted that the porosity of the tablet allows it to disintegrate in the mouth. During the review process there was a number of concerns regarding substance, drug product, process, the

[1] Sponsor's agreement on November 4, 2013, Final FDA acknowledgment on December 8, 2013

biopharmaceutics, and microbiology, hardness, shipping/friability, porosity, and the disintegration times; reviewers. These concerns resulted in a number of exchanged correspondences with the Agency finally satisfied by the sponsor's response to queries concerning these issues. Under the rubric of "Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable" the review notes that :

> "**Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
> The sponsors are advised to continue to find ways to control the tablet hardness and ensure that none of the tablet's hardness falls below (b) (4). This is likely to ensure tablet integrity and dose accuracy for patients. The post approval stability protocol will include, at minimum, first three production batches of each of the strengths and at least one batch of each strength produced during particular calendar year thereafter at a storage condition of 25°C (b) (4) with release time points of every three months in the first year, every six months in the second year, and every year thereafter. As per the packaging master batch record, randomly selected blisters from beginning, middle, and end will be chosen from each of the stability batches. Post approval commitments include stability studies of appropriate number of batches if any changes are made to the product, submission of the stability data in the product annual report, withdrawal of the batches where stability data is found to be outside of acceptable limits, and discussion of occurrence of a single deviation with FDA when the deviation does not affect the safety and efficacy of the product. (b) (4)

Upon requesting clarification as to whether any of any of the phase 4 requests represents a formal 506-B PMR/PMC, Dr. Heimann noted "the post-approval stability commitment is a requirement for approval that is applicable to all new drugs, including generics. It is not a 505-B reportable PMR, and does not go to SRT."

The sponsor has requested that (b) (4) The quality reviewer notes that this designation is inappropriate, and it was a suggestion that the formulation be referred to as a tablet. For reasons described in Section 10 (Other regulatory Issues), I suggested that the formulation should not be designated as a tablet. While dosing forms other than tablet, such as (b) (4) were considered, no consensus could be reached. The Sponsor made additional recommendations for the naming of the formulation, but no Agency consensus could be reached on these additional recommendations. At the times of the writing of this review, as expressed in an email from Ashley Boam to Dr. Heimann and others, sent July 09, 2015, the OPPQ plan appears to be the following:

- "The product dosage form should be called a tablet (thus the nonproprietary name will be: levetiracetam tablets or on the unit dose packet: levetiracetam tablet)."
- "Subsequent to this approval, (b) (4)

[redacted] (b) (4)

3. Nonclinical Pharmacology/Toxicology

Not Applicable.

4. Clinical Pharmacology

The OCP review was performed by Drs. Youm, Krudy and Men.

Two PK studies where performed and are described as follows:

- Study No. LVA-P3-491 (CL-LEV-001-R00), referred to as study 491 in this review: This was a single dose 3-period, 3-sequence, single center, laboratory-blinded, crossover study of comparative bioavailability that compared Levetiracetam [redacted] (b) (4) 1000 mg with 1000 mg Keppra® Film-Coated Tablets in Healthy Male and Female Volunteers under fasting and fed conditions (safety set n = 33).
- Study No. CL-LEV-003 (Novum 11369701), referred to as study 003 in this review: Single-Dose, One-Treatment, One-Period, Open-label study in healthy examining the K of the sponsor's product male and female volunteers under Fasted Conditions (n=12).

Study 491indicated that PK profiles resulting from the administration of fasting Spritam and fasting Keppra IR met routine bioequivalence standards, so that both Cmax and AUC acceptance range of the geometric least square mean ratio 90% CI falls within a 80-125% interval. The comparison of the fed (high fat) single Spritam dose to fasting Keppra IR met bioequivalence standards for AUC, but delayed absorption and also resulted in a 36% reduction in Cmax, which failed the to meet bioequivalence standards. Because of this lack of bioequivalence, the Pharmacometric staff performed simulations to compare fasting Keppra IR and fed Spritam. They observed similar Cmin values, and while the Cmax was less for Spritam, the blood levels for much of the dosing cycle were slightly higher for the Spritam than Keppra IR. Moreover, the concentration/time curves were of similar shape. Because of these factors it was believed that the two situations were therapeutically similar. The reviewer further notes that "studies with Keppra IR have shown that food reduces Cmax 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." Consequently, the reviewers note "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." I agree with these conclusions. It is noteworthy that the division

is most concerned that the Cmax does not fall below that of the RLD as this may be associated with breakthrough seizures. This was not the case. In conclusion, the OCP reviewers believed that these data indicate that the formulation can be considered therapeutically similar to the RLD under fed and fasting conditions. I agree.

The reviewers also examined study 003 which demonstrated that there was no clear trend between the amount of water consumed with the product and its PK profile. Absorption without water was similar, except a in few subjects only experienced delay of on the Tmax of 2.5 hours.

A biopharmaceutical inspection of the clinical and analytical site for the principal study was requested. But, it was decided by the Division of Bioequivalence and GLP Compliance (DBGLPC) that the data is acceptable without an on-site inspection because the Office of Scientific Investigations inspected the sites within the last four year.

5. Clinical Microbiology

This review, which is part of the full CMC review, was performed by J. Cole. A number of issues were discussed between the Microbiology review staff and the Sponsor and information requests issued. The final conclusion was that "the proposed tiered release testing, in conjunction with stability testing, is adequate to assure the microbial safety of this drug product."

6. Clinical/Statistical- Efficacy

Dr. Ramesh Raman performed the medical efficacy review. As there was no controlled trial, there was no clinical statistical review. The determination of efficacy is based upon the efficacy of the RLD, Keppra, described in its label, and the demonstration of Spritam's similar bioavailability to that RLD through the bridging PK studies. Such studies were considered to demonstrate bioequivalence (see Clinical Pharmacology).

7. Safety

Dr. Ramesh Raman performed the medical efficacy review. Like efficacy the determination of safety is based principally upon the safety profile established for the RLD, which is described in its label, and the demonstration of Spritam's similar bioavailability to the RLD. In addition to this, safety data from the two pharmacokinetic studies were examined. Such data, of course, is limited by the small sample size and the fact only single doses were studied.

The additional safety information was derived from two PK studies performed by the Sponsor: 1) Study 491 and 2) Study 003. The designs for these studies are described in the Clinical Pharmacology section.

No deaths or serious adverse events were noted in either study nor discontinuations were observed to result from adverse events.

Dr. Raman notes that in study 491 18 subjects (56.3%) reported 39 adverse events (5 different System Organ Classes and 12 different Preferred Terms) for the test product (Spritam) in a fasting state, 14 subjects (43.8%) reported 20 adverse events after the administration of test product (Spritam) in fed state, and 20 subjects (62.5%) reported 35 adverse events after the administration of reference product in fasting state. Similar percent of patients reported adverse events in study 003. No severe averse events we reported. The most common adverse events reported were related to the nervous system, e.g. somnolence and dizziness. These events are known to be common for the reference product and are labeled. My examination of common adverse events across treatments suggests similarity between the test and reference product.

Dr. Raman notes that no clinically significant effect was observed in ECG assessments, physical examination assessments, vital signs, and neurological examinations during the studies.

8. Advisory Committee Meeting

Not needed.

9. Pediatrics

The product formulation was originally presented to the Division as a (b) (4). As a new formulation product would have been subject to PREA. Based upon this the following was agreed upon with the sponsor as part of an iPSP:

Waivers will be granted for the following populations:

- For patients with partial onset seizures:1) in patients <1month, studies are impossible or highly impractical because of the limited number of patients in these younger populations, 2) in patients 1 month to <4 years, because of inability to dose patients based upon the tablet like formulation and the present mg/kg labeled dosing recommendation for the RLD, and the fact that the product fails to represent a meaningful therapeutic benefit over existing therapies for such patients and is unlikely to be used in a substantial number of patients.

- For patients with juvenile myoclonic epilepsy below 12 years of age, because studies are impossible or highly impractical as a result of the limited population of patients in these ages.
- Primary generalized tonic-clonic seizures under 16 years of age: 1) in patients < 2 years, studies are impossible or highly impractical because of the limited number of patients in these younger populations, 2) for patients 2 years to < (b) (4), because of inability to dose patients based upon the tablet like formulation and the present mg/kg labeled dosing recommendation for the RLD, and the fact that the product fails to represent a meaningful therapeutic benefit over existing therapies for such patients and is unlikely to be used in a substantial number of patients.

According to the iPSP all older pediatric ages will be labeled for the above conditions. No PREA PMRs are necessary. PeRC agreed to the above plan at a June, 10 2015 meeting.

Subsequent to this the sponsor presented an argument for allowing labeling down to 6 years old. The Pharmacometric reviewer concurred with the decision to allow labeling down to the lower age, as did the Division Director. The reader is referred to Dr. Krudys' to the Clinical Pharmacology Addendum Review. This argument is based upon the fact that although dosing is provided in mg/kg[2] the label also notes that "Patients with body weight above 20 kg can be dosed with either tablets or oral solution." Dr. Krudy points that mg/kg dosing would be impractical even for The RLD. Also pointed out is the similarity of PGTC dosing to POS doing. In this case a link of whole tablet to mg/kg dosing can be found for POS in the label where mg/kg and whole tablet dosing are described. In my view the latter issue is questionable, as POS is a different disorder than PGTC. These issues were debated, and it was finally decided to allow whole tablet dosing in the lower age groups.

As the product was finally designated as a tablet, the application no longer triggers PREA as a new dosage form. The final decision was made to designate the product as a tablet (see Other Relevant Regulatory Issues). The DPMH reviewer, Donna Snyder agrees to this.

10. Other Relevant Regulatory Issues

Formulation and Proprietary Name

An issue arose during the review cycle concerning the name of the formulation. The Sponsor requested that it be designated a "(b) (4) This was rejected by CMC, as this does not really represent a "(b) (4) and the designation of "tablet" was suggested. Because the present formulation has unique instructions for administration and a very unique look (large and wide tablet), I expressed concerns about this designation of this product as a "tablet."

[2] The label states: "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 following instructions are contained in the proposed labeling for Spritam:

"… [redacted] the tongue with a dry hand and [redacted] follow [redacted] a sip of liquid [redacted]

These instructions appear to be quite different than the assumed method of the administration for common tablets. Moreover, once this medication is available generically, the product may be freely interchanged with the conventional levetiracetam tablet. Additionally one question raised is, does this mean that patients may administer Spritam as they would common tablets; i.e. swallow whole with a gulp of water, rather than waiting for it to dissolve, and what risk or change in product performance may this lead to. I should note that these products are substantially larger than any ordinary tablet. The Sponsor is developing other products using the same technology, and it is certainly possible that in the future other manufacturers may adapt the same technology. Therefore, there is a potential that the problem may extend beyond the present product.

In her review Dr. Lolita White of DMEPA acknowledges the issue that "if the products are not distinguishable, Spritam and Keppra are vulnerable to confusion in the prescribing, dispensing and administering phases of the medication system." They note if the two products have similar PK profiles "the potential for harm associated with inadvertent wrong product error would be diminished," but also note that "if significant differences exist between the two products, a wrong product error could potentially result in patient harm." They note that they "will defer to DNP regarding the ultimate decision of dosage form designation [redacted] and would like to reserve the option to further evaluate the PI and labeling for risk of medication error once a final decision has been made." My views are described above. The DPMH reviewer, Dr. Donna Snyder, expressed similar concern. This has been further considered and an update discussion of this issue is included in the Product Quality section of this review.

DMEPA performed the proprietary name review and concluded that the proposed proprietary name of Spritam was acceptable.

Financial Disclosure

Dr. Raman notes that the sponsor. Financial Certification and Disclosure form 3454 are provided in the application.

Study 001 was performed by a single principal investigator and 13 sub-investigator and study 003 was performed by a single principal investigator and 3 sub-investigators. The Sponsor submitted a 3454 attesting that the sponsor did not enter into any financial arrangement with the clinical investigator where by the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2. Individual investigator information was also submitted indicating the same.

11. Labeling

See the label included in the approval letter as well as pertinent labeling issues described in the various sections of this review, particularly those related to the formulation name and pediatric labeling.

12. Recommendations

Recommended Regulatory Action: Approval.

Risk Benefit Assessment: The risk and benefit of this new formulation has been demonstrated to be similar to that of approved RLD.

Risk Evaluation and Management Strategies (REMS): No REMSs are necessary.

Postmarketing Requirements (PMRs) and Commitments (PMCs): There are no PMRs.

Recommended Comments to Applicant: Chemistry has standard monitoring requests.

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/s/

NORMAN HERSHKOWITZ
07/28/2015

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	207958
Priority or Standard	Standard
Submit Date(s)	October 1 2014
Received Date(s)	October 1 2014
PDUFA Goal Date	August 1 2015
Division / Office	DNP/OND
Reviewer Name(s)	Ramesh Raman, MD, FACP
Review Completion Date	Jun 1 2015
Established Name	Levetiracetam
(Proposed) Trade Name	Spritam
Therapeutic Class	Anticonvulsant
Applicant	Aprecia Pharmaceuticals
Formulation(s)	Oral Tablets
Dosing Regimen	Variable depending on type of patient population and indication
Indication(s)	Partial Onset Seizures; Myoclonic (Juvenile) Epilepsy; Primary Generalized Tonic-Clonic Seizures
Intended Population(s)	Adults and Pediatrics

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval- subject to approval from all other disciplines and Sponsor's agreement to the proposed label.

1.2 Risk Benefit Assessment

Since the approval of levetiracetam tablets (Keppra) in 1999 (under NDA 21035), the risks associated with levetiracetam and the benefits it can provide is well known and established. The safety profile and the risks associated with Spritam, a different dosage form of levetiracetam, can therefore be considered to be the similar to that of the known risks associated with levetiracetam. Although the purpose of the study that was conducted was to establish the PK comparability of Spritam to the reference drug Keppra and safety assessment was not its primary objective, the safety profile of Spritam from this PK study did not raise any specific clinical safety concerns.

Given its unique dosing and administration attributes, Spritam will provide a new option for high dosing requirements particularly in patients (both adults and pediatric) in whom swallowing tablets is an issue.

Approval of Spritam, with an established safety profile and with its unique dosing form to potentially address swallowing issues in patients with seizures, is therefore justified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Levetiracetam is an antiepileptic drug available as injection, oral solution, immediate release oral tablets and extended release oral tablets. The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide; its molecular formula is C8H14N2O2, and its molecular weight is 170.21 g/mol. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs).

SPRITAM® (levetiracetam (b) (4), is a levetiracetam that is designed to be an easy-to swallow formulation that quickly disperses in the mouth with a sip of the liquid (b) (4). While Spritam exhibits the physical and chemical stability of solid oral dosage preparations, its rapid dispersion in the mouth renders swallowing easy. The (b) (4) dosage form was developed using a three-dimensional printing (3DP) technology.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This 505(b)(2) NDA application submitted on October 1, 2014, supported by PK bridging studies (see section 5 below), relies on the reference listed drug (RLD) Keppra Tablets 1000mg (under NDA 021035) for both non-clinical and clinical data. Reference is made to the March 28, 2013 EOP 2 meeting that provided the direction for the drug development program via the bridging studies. Reference is made to the agreements made during the pre-NDA meeting (meeting May 2014; minutes 6/6/2014) on the content and format of the NDA submission.

As required by PREA, a Pediatric Study Plan was submitted (initial May 21, 2013; revised Sep 12, 2013; final Nov 4, 2013) that was subsequently agreed by the Agency on Dec 8, 2013. The Sponsor does not seek to expand on the already approved RLD's (Keppra's) adult and pediatric indications. Instead a partial waiver that would somewhat be narrower than those for the RLD is requested.

Reviewer comments

The proposed proprietary name "Spritam" was found acceptable by the Agency.

This 505(b)(2) NDA for Spritam- a new dosage tablet form, that relies on Keppra (levetiracetam), the RLD (Reference Listed Drug), aims in establishing its bioequivalence to Keppra for eventual approval. Spritam is intended for patients who are able to swallow tablets made available in the following dosage forms as tablets only- 250 mg, 500 mg, 750 mg and 1000 mg. Spritam must be administered as produced and cannot be bisected or broken into smaller uniform dosage units. Keppra, the RLD, in addition to the oral tablet forms of 250mg, 500 mg, 750 mg and 1000 mg, is available as an oral solution (100mg/mL) for pediatric patients who require dosing that is based

on body weight. Specifically, the oral solution provides the flexibility and the option to titrate the required dose based on body weight particularly in younger patients.

The RLD, Keppra, has approved indications for use in adults and pediatric patients with the following partial waiver in the pediatric sub-population:

- Partial onset seizures in infants less than one month of age (cannot be clearly diagnosed in that population).
- Juvenile myoclonic epilepsy, because it rarely exists below 12 years of age.
- Primary generalized tonic-clonic seizures under 6 years of age, because the number of patients is too small.

The sought indications for Spritam with respect to the type of seizures/epilepsy will be the same as the RLD Keppra. However, because of the lack of an individualized weight-based dosing form of Spritam, a further waiver in those pediatric sub-populations where a weight-based dosing is recommended is requested (as noted above). As noted in the agreed iPSP, this request is justified on the grounds that Spritam as a single dose tablet cannot subserve the needs in a subset of younger patients who require weight based dosing and therefore does not provide a meaningful benefit over existing oral solution products such as Keppra oral solution or other generic oral solution equivalents which are approved for weight based dosing (for patients ≤ 20kg). Granting the requested partial waiver is therefore recommended. If granted, the following will be the pediatric age groups to be waived for Spritam:

- Pediatric patients with partial onset seizures under age 4 years.
- Juvenile myoclonic epilepsy below 12 years of age.
- Primary generalized tonic-clonic seizures under (b)(4) years of age

It is the understanding of this reviewer that the Agency Pediatric Committee has granted the requested waiver.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Reviewer comments

These are acceptable.

3.2 Compliance with Good Clinical Practices

Reviewer Comments

According to the Sponsor, the clinical studies were conducted according to Good Clinical Practices (GCP).

3.3 Financial Disclosures

Reviewer Comments

The submitted Financial Certification and Disclosure information (section 1.3 Administrative Information) and the completed FDA form 3454 is noted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Reviewer's comments

Reference is made to the respective reviews from the other review disciplines.

5 Sources of Clinical Data

The Sponsor conducted clinical PK studies served as the basis for the clinical data. In support of the 505(b)(2) application, Sponsor submitted results from the following two studies:

Study No. LVA-P3-491 (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.
Study No. CL-LEV-003 (Novum 11369701): 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. This study investigated any potential effect on the bioavailability of levetiracetam when taken with no liquid.

5.1 Tables of Studies/Clinical Trials

Table 5.1: Listing of Clinical Studies*

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Pivotal Bioavailability	LVA-P3-491 (CL-LEV-001-R00)	5.3.1.2	Primary -Bioavailability of levetiracetam (b) (4) as compared to Keppra in fasted subjects: -Bioavailability of levetiracetam (b) (4) in fed subjects Secondary -Safety and tolerability of levetiracetam (b) (4) as compared to Keppra Other -Effect of various amounts of water on bioavailability	Single dose bioavailability study in healthy volunteers: -Fasting crossover levetiracetam (b) (4) vs. RLD -Food effect of levetiracetam (b) (4)	Test Products -Levetiracetam (b) (4) 1000 mg -Keppra tablets 1000 mg (RLD) Rout of administration: oral	Total 33 (1 drop out)	Healthy subjects	Single dose (crossover after 7-day washout)	Study Status: Study Complete Type of report: Full study report
Pivotal Pharmacokinetics	11369701 (CL-LEV-003)	5.3.1.1	Pharmacokinetic of levetiracetam (b) (4) taken without water	Single dose, one treatment, one period, open label, fasted	Test Product Levetiracetam (b) (4) 1000 mg Route of administration: oral	12	Healthy subject	Single dose	Study Status: Study Complete Type of report: full study report

*REF: Copied Sponsor's Table 1 Section 2.7.6. Edited for format only.

5.2 Review Strategy

Although there was no formal clinical Phase 3 equivalent or pivotal studies, the clinical safety finings data from the PK studies was the primary focus of this clinical review. In addition, emphasis was placed on the salient findings by the other disciplines if it impacted, if any, the overall recommendation and labeling. These were summarized as appropriate. The studies including the safety findings are discussed under section 5.2. The specific details pertaining to certain PK related aspects such as the PK analytical methodology, modeling, statistical methodology, criteria for relative bioavailability, etc., are not discussed in this review and reference is made to Dr. Yu's review.

5.3 Discussion of Individual Studies/Clinical Trials

Study No. LVA-P3-491 (CL-LEV-001-R00)

Study Title:
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

Study Center:
Algorithme Pharma Inc., 1200 Beaumont Ave., Mount-Royal, Quebec, Canada, H3P 3P1

Phase of Development: Phase I

Study Initiation Date: 2013/10/09

Scheduled Study Completion Date: 2013/10/25

Objectives:
The *primary* objectives of this study were 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 pharmacokinetic profile of levetiracetam (b) (4) 1000 mg. The *secondary* objective of this study was to determine the safety and tolerability of levetiracetam (b) (4) 1000 mg compared to Keppra® film-coated 1000 mg tablets in healthy volunteers.

Methodology:

This was a single center, randomized, single dose, laboratory-blinded, 3-period, 3-sequence, crossover study.

Number of Subjects (Planned and Analyzed):
Planned for inclusion: 33; Included: 33; Drop-out: 1; Analyzed: 32; Considered in the pharmacokinetic and statistical analysis: 32; Considered in the safety analysis: 33

Diagnosis and Main Criteria of Inclusion:
Male and female volunteers, non- or ex-smokers, of at least 18 years of age but not older than 50 years with a body mass index greater than or equal to 18.50 and below 30.00 kg/m2 were included in the study. Subjects were in good health as determined by a medical history, complete physical examination (including vital signs), electrocardiogram (ECG), neurological examination and the usual clinical laboratory tests (hematology, general biochemistry, urinalysis) including negative Human Immunodeficiency Virus (HIV), Hepatitis B and Hepatitis C tests as well as negative screening of alcohol and drugs of abuse in urine and negative beta Human Chorionic Gonadotropin (HCG) qualitative serum pregnancy test (for female subjects).

Test Product (Treatment-1 and Treatment-3), Dose and Mode of Administration, Batch Number:
Name: Levetiracetam
Dosage form/Route of administration: (b) (4) / Oral
Regimen: Single dose of 1 x 1000 mg
Batch no.: LV-13-001

Reference Product (Treatment-2), Dose and Mode of Administration, Batch Number:
Name: Keppra®
Dosage form/Route of administration: Film-Coated Tablet / Oral
Regimen: Single dose of 1 x 1000 mg
Batch no.: 93349

Duration of Treatment:
A single 1000 mg dose of levetiracetam was orally administered in each study period as follows:
Treatment-1: One levetiracetam 1000 mg (b) (4) (Test) was administered in the morning after a 10-hour overnight fast.
Treatment-2: One Keppra® 1000 mg film-coated tablet (Reference) was administered in the morning after a 10-hour overnight fast.
Treatment-3: One levetiracetam 1000 mg (b) (4) (Test) was administered in the morning after a 10-hour overnight fast and thirty minutes after the start of a high-fat, high-calorie breakfast.
The drug administrations were separated by a wash-out of 7 calendar days.

Safety:

Safety was evaluated through assessment of adverse events, standard laboratory evaluations, vital signs, ECG, physical examination and neurological evaluation.

Results

PK Results

See Reviewer's comment below.

Reviewer comments

As noted previously, the only clinical data submitted in support of the 505(b)(2) application stem from the PK studies. These studies have been discussed in detail by Dr. Bei Yu. The following were the conclusions that were summarized by Dr. Yu-

"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 Cmax by 36% for Spritam, which is unlikely to be clinically significant.

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

In addition, Dr. Yu concluded that:

- The PK profiles of levetiracetam were comparable between Spritam and Keppra IR with acceptance range of 90% CI for ratios of two treatments of geometric least squares means for Cmax and AUC falling into BE criteria, 80-125%.
- The administration of Spritam with food would not result in decreased efficacy.
- The volume of water (between 2mL to 30mL- the tested range) would not impact sought the administration of Spritam with a "sip of (b) (4) ".

Safety Results

Reviewer comments

The protocol specified safety assessments and parameters, adverse events definition and related evaluations are noted and appear adequate.

The safety population included all the subjects who entered the study and received at least one of the investigational products under study. 19 males and 14 females, who were predominantly white (81.8%), with a mean weight of 70.0 kg, mean height of 169.0

cms and a mean BMI (kg/m^2) of 24.35 were evaluated and the following is a summary of the safety findings:

- No deaths or serious adverse events occurred during this study.
- Twenty-five (25) (75.8%) of the 33 subjects included in this study experienced a total of 94 adverse events.
- Eighteen (18) subjects (56.3%) reported 39 adverse events (5 different System Organ Classes and 12 different Preferred Terms) after the administration of Treatment-1 (Test Fast), 20 subjects (62.5%) reported 35 adverse events (8 different System Organ Classes and 16 different Preferred Terms) after the administration of Treatment-2 (Reference Fast) and 14 subjects (43.8%) reported 20 adverse events (4 different System Organ Classes and 9 different Preferred Terms) after the administration of Treatment-3 (Test Fed).
- Eighteen (18) subjects (56.3%) experienced adverse events related to the administration of Treatment-1 (Test Fast), 18 subjects (56.3%) experienced adverse events related to the administration of Treatment-2 (Reference Fast) and 11 subjects (34.4%) experienced adverse events related to the administration of Treatment-3 (Test Fed).
- The most frequently observed adverse events experienced by subjects in this study was classified under the System Organ Class “Nervous System Disorders”, i.e. somnolence (16 subjects (50.0%) who received Treatment-1 (Test Fast), 13 subjects (40.6%) who received Treatment-2 (Reference Fast) and 8 subjects (25.0%) who received Treatment-3 (Test Fed)), and dizziness (10 subjects (31.3%) who received Treatment-1 (Test Fast), 6 subjects (18.8%) who received Treatment-2 (Reference Fast) and 3 subjects (9.4%) who received Treatment-3 (Test Fed)).
- The severities of adverse events were mild or moderate. No severe adverse events were observed during the study.
- No subject was withdrawn from the study for safety reasons.
- All serum pregnancy tests were reported negative.
- No clinically significant on-study vital signs, ECG assessments, physical examination assessments, vital signs, and neurological examinations were recorded during this study.

Study No. CL-LEV-003 (Novum 11369701)

Study Title:

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

Design:

Single-Dose, One-Treatment, One-Period, Open-Label Study (Fasted)

Date first subject dosed: 12/28/13
Date last subject completed: 12/29/13

Study Duration: The time from first subject dosed to when the last subject completed was about 1 day.

Objective:

The objective of this study was to characterize the pharmacokinetics 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.

Methodology:

This was a single-dose, one-treatment, one-period, open-label study under fasted conditions. The study was conducted with 12 healthy, adult subjects in accordance with Protocol No. CL-LEV-003 (Revision 0). In this study, a single dose of levetiracetam (b) (4) 1000 mg was administered to subjects following an overnight fast of at least 10 hours. Subjects received the test product as 1 x levetiracetam (b) (4) 1000 mg (Aprecia Pharmaceuticals). Subjects were confined at the clinical facility from at least 10 hours before dosing until after the 24-hour blood sample collection and returned to the clinical facility for a blood sample collection at 36 hours post-dosing. Blood samples were collected at pre-dose and at intervals over 36 hours after dosing.

Subjects:

A total of 12 healthy, non-tobacco using adult subjects were enrolled, and all 12 subjects completed the study. Age= 21-45 years (mean 34 years); Gender= 6M/6F; Race= 1 Caucasian, 7 black, 4 other.

Entry criteria:

All subjects were healthy, non-tobacco using adult subjects who met the inclusion/exclusion criteria for this study.

Drug and Administration:

Levetiracetam (b) (4) (Aprecia pharmaceuticals) 1000mg given orally. This was a single-dose, one-treatment, one-period, open-label study. In this study, a single dose of levetiracetam (b) (4) 1000 mg was administered to subjects following an overnight

fast of at least 10 hours. The study began dosing on 12/28/13 and was completed on 12/29/13.

Safety Analyses:

Adverse events were collected and tabulated. No formal statistical analyses were performed. Other safety assessments included vital signs, ECG, and clinical laboratory.

Results

PK Results

See Reviewer's comment below.

Reviewer comments

According to Dr. Yu, the PK of levetiracetam (b) (4) 1000 mg (Aprecia Pharmaceuticals) in this study (no water provided during drug administration procedure) were 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- as noted above), though the median Tmax tended to be longer in this study (0.92 versus 0.58 hours).

Safety Results

Reviewer comments

The protocol specified safety assessments and parameters, adverse events definition and related evaluations are noted and appear adequate. The subjects were monitored throughout the study for any adverse experiences. Adverse events were collected through both solicited and unsolicited means and were subsequently coded in tabular form using the MedDRA Version 16.0 adverse event dictionary. The subjects were encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each adverse event was determined by the clinic staff based on observation and questioning of the subject. The Investigator judged the relationship of the event to the study treatments.

- There were no deaths or serious AE or significant AE reported.
- No subject was withdrawn from the study for safety reasons.
- There were no AE localizable to the dosing site.
- Seven (7) adverse events were reported by 6 of the 12 subjects who participated in this study. All reported adverse events were considered "mild" and resolved spontaneously by study completion. The most frequently reported adverse event for the test product was dizziness (2 subjects).

- All pregnancy tests were reported negative.
- No clinically significant on-study vital signs, ECG assessments, physical examination assessments, vital signs, and neurological examinations were recorded during this study.
- Post-study hematology and chemistry assessment of blood collected at the time of the last pharmacokinetic blood sample collection of the study were within 20% of the normal range and were determined not clinically significant or upon repeat analysis considered not clinically significant by the Investigator.

6 Review of Efficacy

Reviewer comments

There were no efficacy studies or data that was collected.

7 Review of Safety

Reviewer comments

See section 5.3.

7.3 Major Safety Results

See section 5.3. There were no reported deaths or serious adverse events or discontinuations or withdrawal due to adverse events.

7.4 Supportive Safety Results

See section 5.3.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

None submitted (as agreed during the pre-NDA meeting- minutes of 6-6-2014).

9.2 Labeling Recommendations

Please refer to separate label review.

9.3 Advisory Committee Meeting

Not applicable.

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/s/

RAMESH RAMAN
07/28/2015

NORMAN HERSHKOWITZ
07/28/2015