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*APPLICATION NUMBER:*

**207958Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	7/24/2015
<b>From</b>	Angela Yuxin Men., MD PhD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	NDA 207958
<b>Applicant</b>	Apreece Pharmaceuticals Company
<b>Date of Submission</b>	10/1/2014
<b>PDUFA Goal Date</b>	8/1/2015
<b>Proprietary/ Established (USAN) Name</b>	SPRITAM (levetiracetam) (b) (4)
<b>Dosage forms / Strength</b>	250 mg, 500 mg, 750 mg, 1000 mg
<b>Proposed Indication(s)</b>	Partial Onset Seizures; Myoclonic Seizures In Patients With Juvenile Myoclonic Epilepsy; Primary Generalized Tonic-Clonic Seizures
<b>Recommended:</b>	Approval

### 1. Introduction

Apreece Pharmaceuticals Company (Sponsor) is seeking an approval for SPRITAM (levetiracetam (b) (4) product), which is an easy-to-swallow formulation that quickly disperse in the mouth with a sip of liquid. SPRITAM can provide an alternative to high-dose traditional Keppra tablets, which aid in patient compliance and ease of dosing for those who have difficulty swallowing large traditional tablets or capsules.

The sponsor submitted this NDA under 505 (b)(2) using KEPPRA (levetiracetam) immediate release (IR) tablets as the reference listed drug (RLD). In this submission, without conducting efficacy trial, the sponsor submitted two clinical pharmacology studies to support its approval: a BA/BE study (Study LVA-P3-439/CL-LEV-001-R001) bridging SPRITAM and the RLD, and a PK study (Study CL-LEV-003/ Novum 11369701) evaluating levetiracetam PK following administration of SPRITAM without taking water. This information will support the proposed SPRITAM (levetiracetam (b) (4)) product indications, which are the same as the currently approved indications for the RLD, KEPPRA tablets for oral use.

- Partial Onset Seizures: Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children (b) (4) years of age and older with epilepsy.
- Myoclonic Seizures In Patients With Juvenile Myoclonic Epilepsy: Levetiracetam is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy.
- Primary Generalized Tonic-Clonic Seizures: Levetiracetam is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.

The followings are the key primary reviewers for this NDA207958:

- **Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Application Technical Lead	Mansoor Khan	OTR/Division of Product Quality Research
Drug Substance	Martha Heimann	ONDP/Division of New Drug Products I/Branch I
Drug Product	Thomas Wong	ONDP/Division of New Drug Products I I/Branch I
Process	Akm Khairuzzaman	OPF/Division I/Branch I
Microbiology	Jessica Cole	OPF/Division IV/Branch III
Facility	Vibhakar Shah	OPPQ/Division of Internal Policies and Programs/Branch II
Biopharmaceutics	Maziar Kakhi	ONDP/Division of Biopharmaceutics/Branch I
OTR Representative	Ziyaur Rahman	OTR/Division of Product Quality Research
Labeling	Andrei Ponta	ONDP/Division of New Drug Products I/Branch I
Project/Business Process Manager	Teshara G. Bouie	OPRO/Division II/Branch IV

- Clinical: Dr. Ramesh Raman MD, (Team Leader: Norman Hershkowitz, M.D., Ph.D.)
- DPMH: Donna L. Snyder, MD (Team Leader: Hari Cheryl Sachs, MD, Director: Lynne Yao, MD)
- Clinical Pharmacology: Bei Yu, Ph.D. (Team Leader: Angela Yuxin Men, M.D., Ph.D.; PM Team Leader: Kevin Krudys, Ph.D.)
- DMEPA: Lolita White, PharmD (Team Leader: Danielle Harris, PharmD, BCPS)
- Project Manager: Cathleen Michaloski, BSN, MPH, RAC

## 2. Regulatory Background

Three milestone meetings were held for Aprecia submitted background materials, a Type B Pre-IND, an EOP2 and a pre-NDA meeting. An End of Phase II Meeting was held on March 28, 2013 to discuss the overall plan of development for the product, and a preNDA Meeting was held on May 8, 2014 to establish the expected format and content of the SPRITAM NDA prior to its submission and to obtain FDA guidance and agreement several key CMC and clinical issues.

Aprecia expected to submit levetiracetam (b) (4) (SPRITAM) as the first NDA for a 3DP-based product, intended for submission under Section 505(b)(2).

### 3. CMC

Final recommendation from the CMC review team is to approve SPRITAM with the following Phase 4 commitment:

- 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)

#### Drug Substance/Levetiracetam Quality Summary

Levetiracetam is a well characterized, small molecule that is the subject of four NDAs for IR tablets, extended-release tablets, oral solution, and injection under the trade name Keppra already.

#### Drug Product Quality Summary

The sponsor applied a novel forming technique known as Three Dimensional Printing ("3DP") for high dose of levetarecitam, which is unlike orally disintegrating tablets which are usually meant for low dose drugs. Aprecia's (b) (4) are highly porous structures designed and formulated to balance adequate strength for general handling while maintaining the ability to disperse instantly when exposed to a sip of (b) (4).

A number of concerns from a CMC perspective, such as substance/drug product process, microbiology, hardness, shipping/friability, porosity, and the disintegration times etc., were satisfied with the sponsor's responses to queries. Throughout the reviews and inspection process, the sponsors have used the term (b) (4)" and the quality reviewers have used the term "tablets" for these 3D printed dosage forms. According to older versions of USP, a

(b) (4)  
After several rounds discussion internally and with the sponsor, the Agency proposed the dosage form as "tablets". At the times of the writing of this review, however, the sponsor now is trying to justify calling the product (b) (4) per the t-con held on July 24, 2015. Please refer the final labeling regarding the definitive term used for this product.

## 4. Nonclinical Pharmacology/Toxicology

There is no updated information.

## 5. Biopharmaceutics

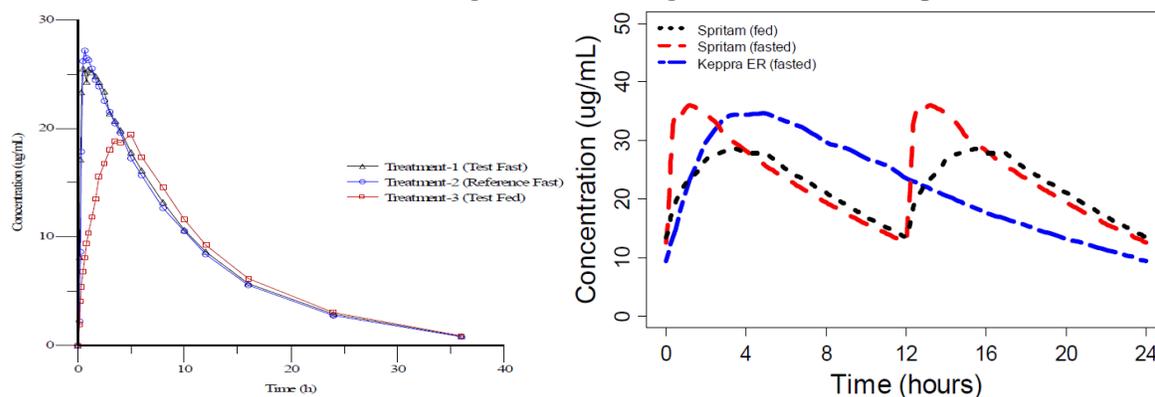
Levetiracetam is a BCS class 1 drug (high solubility, high permeability per Keppra labels). No new Biopharmaceutics information is available in this submission.

## 6. Clinical Pharmacology

The sponsor submitted a 505b2 application relying on Keppra® as the RLD that included two studies:

- A single dose comparative fasted and fed bioavailability, bioequivalence (BA/BE) study comparing 1000 mg levetiracetam (b)(4) to 1000 mg Keppra® in healthy male and female volunteers (pivotal PK study)
- A pharmacokinetic study of a test formulation of 1000 mg levetiracetam (b)(4) in healthy male and female volunteers

Following SPRITAM administration at 1000 mg in healthy subjects, it showed SPRITAM has 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<sub>max</sub> by 36% for SPRITAM. In order to determine how much change of C<sub>max</sub> at steady-state, simulations using nonparametric superposition (right Figure below) 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 trough concentration is comparable 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. In addition, over a substantial portion of the day (~13 to 24 hours), levetiracetam concentrations in the fed state are actually higher than the concentrations for a regimen that has established efficacy (extended release levetiracetam). Therefore, we do not think such T<sub>max</sub> and C<sub>max</sub> changes will have significant clinical impact.



Left Figure: 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

Right Figure: 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)

There is no clear trend or correlation observed between the amount of water ingested with SPRITAM and the PK parameters. SPRITAM should be taken with a sip of (b) (4).

*Note:* The clinical and analytical site inspection for the pivotal PK study was requested. But Division of Bioequivalence and GLP Compliance (DBGLPC) concluded that the data is acceptable without an on-site inspection because the Office of Scientific Investigations inspected the sites within the last four year.

Dr. Krudys also wrote an addendum to explain how the dosing information in the KEPPRA label for pediatric patients with partial onset seizures (POS) to infer the intended tablet dosing in PGTC patients (See Section 9 for detailed rationale).

In summary, Drs. Yu, Krudys and Men reviewed the submission and the team recommends approval of SPRITAM from an OCP perspective.

## 7. Efficacy

There is no clinical efficacy trial conducted. SPRITAM should have similar efficacy as that of RLD, Keppra® IR tablets, as they have equivalent rate and extent of absorption.

## 8. Safety

Drs. Raman and Hershkowitz reviewed the safety information obtained from PK studies and there were no severe AEs, nor death, were noted. Please note that only single dose was administered in the PK studies and the sample size, therefore, is small. But, SPRITAM safety profile can be established using the information obtained from RLD, which is described in its label, as SPRITAM and RLD have equivalent rate and extent of absorption.

Dr. Raman found that the most common adverse events reported for PK studies were related to the nervous system, e.g. somnolence and dizziness. These events are known to be common for KEPPRA as well. In addition, there was no clinically significant effect observed in ECG assessments, physical examination assessments, vital signs, and neurological examinations during the studies.

Clinical team recommends approval of SPRITAM.

## 9. Advisory Committee Meeting

None

## 10. Pediatrics

At the time of the EOP2 meeting took place between DNP and the sponsor March 28, 2013, the product was considered to be a new dosage form, and as a result, triggered a pediatric assessment under the Pediatric Research and Equity Act (PREA). The sponsor submitted a Pediatric Study Plan on November 4, 2013, which included an agreed plan to request partial waivers for the following pediatric subpopulations on the grounds that studies are impossible or highly impractical:

- POS in infants less than 1 month of age because the condition cannot be diagnosed in this neonatal population
- Juvenile myoclonic epilepsy, because the condition rarely exists below 12 years of age
- PGTC seizures because the number of patients under 6 years of age is too small to study

In addition, the Agreed iPSP included a plan for waivers in pediatric patients who require weight based dosing on 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. These patients can use the existing oral solution.

At the completion of the review, CMC had determined that this dispersible tablet should be designated as a tablet. Then SPRITAM will no longer trigger PREA as a new dosage form. Therefore, no PMRs were planned under PREA, which was agreed at a June, 10 2015 PERC meeting.

On July 2, 2015, the sponsor sent in a response and argued that the dosing of pediatric patients with Primary Generalized Tonic-Clonic Seizures (PGTCS) is adequately supported based upon the labeling and supporting studies of the listed drug, KEPPRA, down to 6 years old with body weight above 20 kg. Dr. Krudys wrote a Clinical Pharmacology Addendum Review and agreed with the sponsor's proposal.

## 11. Labeling

See labeling included in the Divisions action letter.

DMEPA also reviewed the revised Commercial Carton Labeling, Physician Sample Carton Labeling, Physician Sample Blister Label, Commercial Blister Label and concluded that they are acceptable from a medication error perspective.

## 12. Recommended Regulatory Action

The Sponsor's submission provides adequate information for regulatory approval.

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/s/  
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YUXIN MEN  
07/25/2015