CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207958Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA #/Supplement #	207958
Applicant Name	Aprecia Pharmaceuticals
Date of Submission	10/1/14
PDUFA Goal Date	8/1/15
Proprietary Name/ Established (USAN) Name	Spritam/levetiracetam
Dosage Forms/Strength	Oral tablets/250 mg, 500 mg, 750 mg, and 1000 mg
Proposed Indication(s)	Adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy 4 years of age and older weighing more than 20 kg, myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ramesh Raman, MD; Norm Hershkowitz, MD, PhD
Statistical Review	N/A
Pharmacology Toxicology Review	N/A
CMC/OBP Review	Mansoor Khan, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Bei Yu, PhD; Kevin Krudys, PhD
OPDP	Aline Moukhtara, RN, MPH
OSI	Shila Nkah
CDTL Review	Angela Men, MD, PhD
OSE/DMEPA	Lolita White, PharmD
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	Twanda Scales, RN, MSN
PMHS	Donna Snyder, MD
SEALD	N/A
Other	N/A

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Introduction

Keppra (levetiracetam) is an approved drug product as adjunctive therapy in the treatment of partial onset seizures in adults and children 1 month of age and older with epilepsy, myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.

Aprecia Pharmaceuticals (Aprecia) has submitted a 505(b)(2) application for the approval of a proprietary presentation of levetiracetam (with a proprietary name of Spritam) for the treatment of the same indications (in similar populations with similar dosing) as Keppra. Spritam is intended to provide rapid and easy swallowing, as it is manufactured using a three-dimensional printing process that allows for rapid dispersion in the mouth when taken with a small amount of (b) (4). Keppra is the reference listed drug for this application. In addition to the established safety and effectiveness of Keppra, the application relies on the usual array of supportive data and the results of clinical pharmacology studies.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

Keppra was initially approved in 1999. Various supplements extended its indications to those described above. Keppra is available as 250 mg, 500 mg, 750 mg, and 1000 mg tablets.

It is somewhat notable that, as far as the Division knows, Spritam will be the first approved product manufactured using three-dimensional printing.

As discussed in the various reviews, the appropriate name for the dosage form has been a source of some consideration at various levels of the Agency throughout the review process, prompted by the novel manufacturing process. Ultimately, a designation of "tablet" has been applied for this application.

3. CMC/Device

Dr. Khan recommends approval. As the new three-dimensional printing process produces highly porous tablets that may be susceptible to breakage, especially during shipping and handling, the CMC team has had discussions with the sponsor concerning the need for post-approval surveillance for breakage. (b) (4) A biowaiver for the 250 mg, 500 mg, and 750 mg tablets has been granted. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no other CMC issues.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

The sponsor submitted two clinical pharmacology studies intended to establish the bioequivalence of Spritam with the reference listed drug, Keppra.

The first study was intended to establish the comparative bioavailability of Spritam 1000 mg and Keppra 1000 mg under fasting conditions, along with an evaluation of food effect. As discussed in detail by Drs. Yu, Men, Krudys, and Hershkowitz, at 1000 mg, Spritam was bioequivalent to Keppra under fasted conditions. There was no effect of food on AUC, but Cmax was delayed by 36%. In order to explore the clinical impact of this Cmax delay, simulations were performed that established a reduced Cmax delay in the presence of food at steady state vs. a single dose, similar concentration-time curve shapes in the fed and fasted states, including similar Cmin values (of importance in epilepsy to help prevent breakthrough seizures), and concentrations of Spritam in the fed state of known efficacious values. The team also points out that if a formal bioequivalence study had been performed in the fed state, it is likely that bioequivalence would have been demonstrated, given that Keppra itself has a 20-30% reduction in Cmax when given with food, only slightly less than Spritam. For these, reasons, the team views Spritam as comparable and therapeutically similar to Keppra under both fasted and fed conditions.

The second study evaluated the influence of the amount of water consumed with Spritam on its pharmacokinetic characteristics. As Dr. Men notes, there was no clear trend or correlation observed between the amount of water ingested and pharmacokinetic parameters.

Dr. Krudys's review addendum describes the regulatory history of weight-based dosing in pediatric patients 6 years of age and older with primary generalized tonic-clonic seizures with regard to the dosing described in approved labeling for Keppra and the proposed dosing for Spritam. I refer to his review for a detailed discussion of this issue and agree with his conclusions and recommendations for whole tablet weight-based dosing in pediatric patients 6 years of age and older with primary generalized tonic-clonic seizures. This recommendation is based, in part, on the dosing described for partial onset seizures. Dr. Hershkowitz points out that partial onset seizures are different than generalized tonic-clonic seizures, which may imply that differing doses may be needed. I agree that this may be true, but the approach described by Dr. Krudys is consistent with that already described in Keppra labeling, and should be acceptable for Spritam, given its therapeutic equivalence to Keppra.

The Office of Scientific Investigations determined that on-site inspection of the clinical pharmacology sites was not needed as the sites had recently been inspected and found to be acceptable.

I concur with the conclusions reached by Drs. Yu, Men, and Krudys that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Efficacy is addressed by assessment of bioequivalence to Keppra. There are no new efficacy data.

8. Safety

Safety is addressed primarily by assessment of bioequivalence to Keppra. In addition, Dr. Raman reviewed the safety observations from the clinical pharmacology studies and concluded that they were consistent with the known safety profile of Keppra as described in approved labeling. Dr. Hershkowitz also examined these data and reached the same conclusion.

I concur with the conclusions reached by Drs. Raman and Hershkowitz that there are no outstanding safety issues that preclude approval.

9. Advisory Committee Meeting

N/A

10. Pediatrics

Spritam was discussed at a pediatric review committee (PeRC) meeting on June 10, 2015, and agreed with the Division that there will be no postmarketing requirements for additional pediatric studies as Spritam is not a new dosage form.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

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

13. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

The sponsor has provided substantial evidence of effectiveness for the use of Spritam as adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy 4 years of age and older weighing more than 20 kg, myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy, based on an acceptable demonstration of therapeutic equivalence to Keppra, which we have previously approved for these indications. There are no new safety concerns associated with the use of Spritam in these populations. There are no outstanding unresolved issues.

There are no necessary postmarketing requirements or commitments.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of Spritam as adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy 4 years of age and older weighing more than 20 kg, myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.

For these reasons, I will issue an approval letter for this application, to include the agreed-upon product labeling.

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

/s/

WILLIAM H Dunn
07/30/2015