CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207958Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs – ODE IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

MEMORANDUM AND PEDIATRIC LABELING REVIEW

Date Consulted: January 16, 2015

From: Donna L. Snyder, MD
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Pediatric Team Leader
Lynne Yao, MD, Acting Division Director
Division of Pediatric and Maternal Health (DPMH)

To: The Division of Neurology Products (DNP)

Drugs: Spritam™ (levetiracetam),
250 mg, 500 mg, 750 mg and 1000 mg tablets

NDA: 207958

Applicant: Aprecia Pharmaceuticals

Proposed indications:

- Treatment of Partial Onset Seizures (POS) in Patients 4 years of age and older and at least 20 kg
- Treatment of Myoclonic Seizures in Patients 12 years of age and older
- Treatment of Primary Generalized Tonic Clonic (PGTC) Seizures in Patients (b) (4) years of age and older

Materials Reviewed:

- Proposed Spritam™ (levetiracetam) labeling submitted, March 4, 2015
- End of Phase 2 Meeting Minutes from March 28, 2013, dated April 26, 2013, DARRTS Reference ID: 3299279

- Pediatric Review Committee (PeRC) meeting minutes, from PeRC meeting on July 17, 2013, dated October 17, 2014, DARRTS Reference ID: 3391905
- Agreed iPSP for partial onset seizures (POS), juvenile myoclonic epilepsy and primary generalized tonic clonic (PGTC) seizures, dated December 8, 2013, DARRTS Reference ID: 3418101
- Division of Medication Error Prevention and Analysis (DMEPA) review, dated May 26, 2015, DARRTS Reference ID: 3762997
- Clinical Pharmacology Review of the application, dated June 5, 2015, DARRTS Reference ID: 3775548

Consult Request:
To assist the Division in the review of a 505b2 NDA application for a new levetiracetam tablet using Keppra® (levetiracetam) IR as the reference listed drug (RLD).

Background and Regulatory History:
Levetiracetam (b) (4) (Spritam™) is a tablet form of levetiracetam that disperses in the mouth after a sip of (b) (4) is given. The sponsor has submitted a 505(b)(2) application for the product that relies on the reference listed drug (RLD) Keppra®.

An End of Phase 2 meeting took place between DNP and the sponsor March 28, 2013. At the time of the meeting, 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 was advised at the End of Phase 2 meeting that under the Food and Drug Administration Safety and Innovation Act (FDASIA), sponsors are required to submit an initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 meeting (or other agreed upon time for products that have not had an EOP2 meeting). After negotiations with the Division, the sponsor submitted an agreed Pediatric Study Plan on November 4, 2013.

The Agreed iPSP includes a 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

The Agreed iPSP includes 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. Weight based dosing is recommended for pediatric patients under 4 years of age or under 20 kg with POS and pediatric patients under (b) (4) years of age with PGTC seizures. For PGTC seizures, the

clinical studies for the initial approval were done using weigh-based dosing and data was not collected to support dosing with a fixed-dose product.

Reviewer comment: With the exception of the partial waivers related to weight-based dosing, these waivers are similar to the waivers granted for Keppra®, the RLD. More recent waivers for PGTC seizure products have required studies down to 2 years of age. However for this product, DNP agreed studies are not necessary because this fixed dose product would be inappropriate for pediatric patients 2 and 6 years of age who likely would require weight based dosing. DNP met with PeRC on July 17, 2013 to discuss the iPSP. PeRC agreed by a close vote that the proposed waivers above were acceptable.

Pediatric studies using Spritam likely not be required because the product will rely on Keppra for labeling and since Keppra is approved in pediatric patients, the product will be fully assessed for pediatric patients able to be dosed using the tablet, as long as bioequivalence is established between the RLD and Spritam™.

Reviewer comment: Since the application was submitted, CMC (chemistry and manufacturing controls) has determined that this dispersible tablet should be designated as a tablet (email communication, Martha Heimann, May 28, 2015). The Division of Medication Error Prevention and Analysis (DMEPA) is concerned that if the product is designated as a tablet, that the products will be confused in the "prescribing, dispensing and administrating phases of the medication system." DNP and DPMH share this concern and the issue is still under discussion within the Agency. If the product is designated a tablet, then it will no longer trigger PREA as a new dosage form. Regardless of the dosage form designation, labeling will be unaffected. No PMRs were planned under PREA.

Studies submitted to support the application:
On October 1, 2014, 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
- A pharmacokinetic study of a test formulation of 1000 mg levetiracetam (b) (4) in healthy male and female volunteers

The sponsor did not submit any efficacy studies as part of the application, since they are relying on the efficacy of the RLD.

Reviewer comment: The Office of Clinical Pharmacology (OCP) agreed that the submitted studies supported approval of the application from a clinical pharmacology perspective. OCP determined that efficacy was not impacted by food. The PK was similar when the product was taken with or without water, however the T_{max} was prolonged. OCP determined that taking the product without water could delay drug absorption as long as 5-6 hours and recommended that Spritam™ should be taken with

(b) (4). *However, OCP also determined that the volume of* (b) (4) *was not critical, and that including instructions to take the product with a "sip of* (b) (4) *" was sufficient for drug administration.*

DNP consulted the Division of Pediatric and Maternal Health (DPMH) to participate in meetings related to the review of the application, assist with preparation of paperwork for presentation of the pediatric assessment to the Pediatric Review Committee (PeRC), and to provide input on pediatric labeling.

This review provides suggested revisions and structuring of existing information related to the 8.4 (Pediatric Use) and 14.2 (Clinical Studies) in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

DISCUSSION: PEDIATRIC USE LABELING

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

The sponsor submitted Keppra® labeling as the proposed labeling for this product. Since this product will only be indicated for pediatric patients who can be dosed using tablets, the indications, dosing and clinical studies for indications that require weight-based dosing have been removed from labeling. (b) (4) Our recommendations reflect labeling shared with the Division on June 4, 2015 and may differ from the final version of labeling that is negotiated with the sponsor. See the approval letter for the final version of labeling.

DPMH –RECOMMENDATIONS FOR LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

————INDICATIONS AND USAGE————

SPRITAM is indicated for adjunctive therapy in the treatment of:

- Partial onset seizures in patients 4 years of age and older weighing more than 20 kg with epilepsy (1.1)
- Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy (1.2)
- Primary generalized tonic-clonic seizures in patients (b) (4) years of age and older with idiopathic generalized epilepsy (1.3)

—DOSAGE AND ADMINISTRATION ——

Administer SPRITAM tablets (b) (4) (2.1)

Partial Onset Seizures

- *4 Years (b) (4) weighing 20 to 40 kg:* 250 mg twice daily, increase by 250 mg twice daily to a maximum of 750 mg twice daily (2.2)
- (b) (4)
- (b) (4) *of age and older:* 500 mg twice daily, increase as needed and tolerated by 500 mg twice daily every 2 weeks to a maximum recommended dose of 1500 mg twice daily (2.2)

Myoclonic Seizures in Adults and Pediatric Patients 12 Years of Age and Older

- 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.3)

Primary Generalized Tonic-Clonic Seizures in Patients (b) (4) years of Age and Older

- 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily (2.4)

1 INDICATIONS AND USAGE

1.1 Partial Onset Seizures

SPRITAM is indicated as adjunctive therapy in the treatment of partial onset seizures in patients 4 years of age and older weighing more than 20 kg with epilepsy.

1.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

SPRITAM is indicated as adjunctive therapy in the treatment of myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy.

1.3 Primary Generalized Tonic-Clonic Seizures

SPRITAM is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients (b) (4) years of age and older with idiopathic generalized epilepsy.

Reviewer comment: Indications and age ranges were removed that required weight-based dosing.

2 DOSAGE AND ADMINISTRATION

2.2 Partial Onset Seizures

Adults and Pediatric Patients (b) (4) Years of Age and Older

Initiate SPRITAM with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. There is no evidence that doses greater than 3000 mg/day confer additional

benefit.

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

For SPRITAM 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).

(b) (4)

2.3 Myoclonic Seizures in Patients 12 Years of Age and Older with Juvenile Myoclonic Epilepsy

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 studied.

2.4 Primary Generalized Tonic-Clonic Seizures in Patients (b) (4) 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.

Reviewer comment: Dosing for indications that required weight-based dosing were removed as well as any references to use of the oral solution.

8 Use in Specific Populations

8.4 Pediatric Use

SPRITAM is not recommended for pediatric patients where weight-based dosing is required. Other levetiracetam products are available for pediatric patients that require weight-based dosing.

Partial Onset Seizures

The safety and effectiveness of SPRITAM have been established in the adjunctive treatment of partial onset seizures in pediatric patients 4 years of age and older with epilepsy. Use is based on controlled studies in adult patients and efficacy data in 198 pediatric patients 4 to 16 years of age treated with levetiracetam with partial onset seizures [*see Clinical Studies (14.1)*].

A 3-month, randomized, double-blind, placebo-controlled study was conducted to assess the neurocognitive and behavioral effects of levetiracetam as adjunctive therapy in 98 (levetiracetam N=64, placebo N=34) pediatric patients, 4 to 16 years of age, with partial seizures that were inadequately controlled. The target dose was 60 mg/kg/day. Neurocognitive effects were measured by the Leiter-R Attention and Memory (AM) Battery, which measures various aspects of a child's memory and attention. Although no substantive differences were observed between the placebo and drug treated groups in the median change from baseline in this battery, the study was not adequate to assess formal statistical non-inferiority of the drug and placebo. The Achenbach Child Behavior Checklist (CBCL/6-18), a standardized validated tool used to assess a child's competencies and behavioral/emotional problems, was also assessed in this study. An analysis of the CBCL/6-18 indicated on average a worsening in levetiracetam-treated patients in aggressive behavior, one of the eight syndrome scores.

Myoclonic Seizures

The safety and effectiveness of SPRITAM have been established as adjunctive treatment of myoclonic seizures in pediatric patients 12 years of age and older with juvenile myoclonic epilepsy. Use is based on one controlled study that included 113 adult and pediatric patients as young as 12 years of age treated with levetiracetam with juvenile myoclonic epilepsy [*see Clinical Studies (14.2)*].

Primary Generalized Tonic-Clonic Seizures

The safety and effectiveness of SPRITAM have been established as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in pediatric patients 16 years of age and older with idiopathic generalized epilepsy. Use is based on one controlled study that included 164 adult and pediatric patients treated with levetiracetam with generalized tonic clonic seizures [*see Clinical Studies (14.3)*].

Juvenile Animal Studies

Studies of levetiracetam in juvenile rats (dosing from day 4 through day 52 of age) and dogs (dosing from week 3 through week 7 of age) at doses of up to 1800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m^2 basis) did not indicate a potential for age-specific toxicity.

Reviewer comment: Pediatric Use was revised to include the approved indications for this product and to note that other formulations are available for pediatric patients that require weight-based dosing. The subsection was reorganized to include information for each indication under a subheading in order to improve readability.

14 CLINICAL STUDIES

14.1 Partial Onset Seizures

Effectiveness in Partial Onset Seizures in Pediatric Patients 4 to 16 Years of Age with Epilepsy

The effectiveness of levetiracetam as adjunctive therapy (added to other antiepileptic drugs) in pediatric patients was established in one multicenter, randomized double-blind, placebo-controlled study (Study 4), conducted at 60 sites in North America, in pediatric patients 4 to 16 years of age with partial seizures uncontrolled by standard antiepileptic drugs (AEDs). Eligible patients on a stable dose of 1-2 AEDs, who still experienced at least 4 partial onset seizures during the 4 weeks prior to screening, as well as at least 4 partial onset seizures in each of the two 4-week baseline periods, were randomized to receive either levetiracetam or placebo. The enrolled population included 198 patients (levetiracetam N=101, placebo N=97) with refractory partial onset seizures, whether or not secondarily generalized. The study consisted of an 8-week baseline period and 4-week titration period followed by a 10-week evaluation period. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly partial seizure frequency relative to placebo over the entire 14-week randomized treatment period (titration + evaluation period). Secondary outcome variables included the responder rate (incidence of patients with ≥ 50% reduction from baseline in partial onset seizure frequency per week). **Error! Reference source not found.** displays the results of this study.

Table 1: Reduction In Mean Over Placebo In Weekly Frequency Of Partial Onset Seizures in Study 4

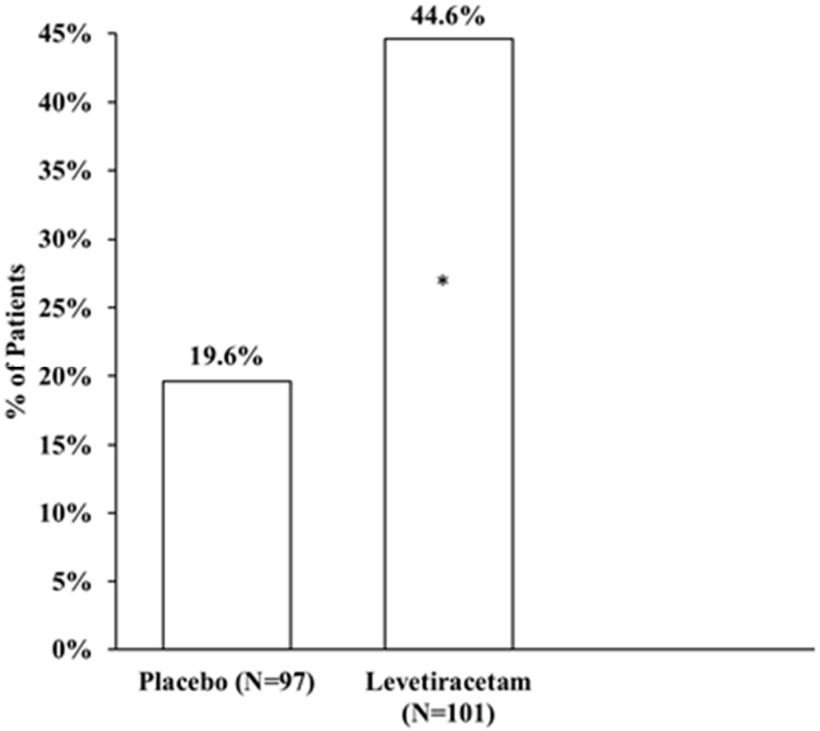
	Placebo (N=97)	**Levetiracetam (N=101)**
Percent reduction in partial seizure frequency over placebo	**–**	**26.8%[i)]**

Error! Reference source not found. statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥ 50% reduction in weekly seizure rates from baseline in partial onset seizure frequency over the entire

randomized treatment period (titration + evaluation period) within the two treatment groups (x-axis) is presented in **Error! Reference source not found.**.

Figure 1: Responder Rate (≥ 50% Reduction From Baseline) in Study 4



***statistically significant versus placebo**

14.3 Primary Generalized Tonic-Clonic Seizures

Effectiveness in Primary Generalized Tonic-Clonic Seizures in Patients (b) (4) Years of Age and Older

The effectiveness of levetiracetam as adjunctive therapy (added to other antiepileptic drugs) in patients16 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic (PGTC) seizures was established in one multicenter, randomized, double-blind, placebo-controlled study (Study 7), conducted at 50 sites in 8 countries. Eligible patients on a stable dose of 1 or 2 antiepileptic drugs (AEDs) experiencing at least 3 PGTC seizures during the 8-week combined baseline period (at least one PGTC seizure during the 4 weeks prior to the prospective baseline period and at least one PGTC seizure during the 4-week prospective baseline period) were randomized to either levetiracetam or placebo. The 8-week combined baseline period is referred to as "baseline" in the remainder of this section. The population included 164 patients (levetiracetam N=80, placebo N=84) with idiopathic generalized epilepsy (predominately juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening) experiencing primary generalized tonic-clonic seizures. Each of these syndromes

of idiopathic generalized epilepsy was well represented in this patient population. Patients were titrated over 4 weeks to a target dose of 3000 mg/day and treated at a stable dose of 3000 mg/day over 20 weeks (evaluation period). Study drug was given in 2 equally divided doses per day.

The primary measure of effectiveness was the percent reduction from baseline in weekly PGTC seizure frequency for levetiracetam and placebo treatment groups over the treatment period (titration + evaluation periods). There was a statistically significant decrease from baseline in PGTC frequency in the levetiracetam-treated patients compared to the placebo-treated patients.

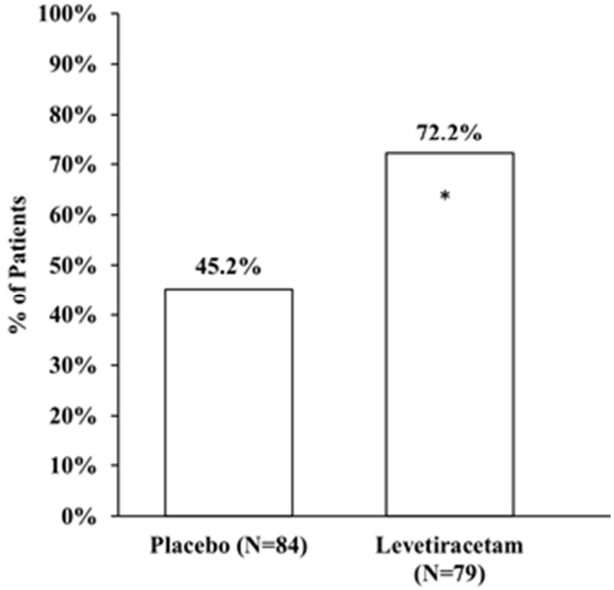
Table 2: Median Percent Reduction From Baseline In PGTC Seizure Frequency Per Week in Study 7

	Placebo (N=84)	**Levetiracetam (N=78)**
Percent reduction in PGTC seizure frequency	**44.6%**	**77.6%[i)]**

Error! Reference source not found. statistically significant versus placebo

The percentage of patients (y-axis) who achieved ≥ 50% reduction in weekly seizure rates from baseline in PGTC seizure frequency over the entire randomized treatment period (titration + evaluation period) within the two treatment groups (x-axis) is presented in **Error! Reference source not found.**.

Figure 2: Responder Rate (≥ 50% Reduction From Baseline) In PGTC Seizure Frequency Per Week in Study 7



*statistically significant versus placebo

Reviewer comment: The sponsor proposed retaining information in labeling for pediatric studies for POS in ages 1 month to (b) (4) years of age and for pediatric patients 6 to (b) (4) years of age with PGTC seizures. DPMH removed the section describing studies in pediatric patients 1 month to 4 years of age with POS that require weight-based dosing, and any references to weight-based dosing in studies of pediatric patients 4 to (b) (4) years of age with POS. Studies in PGTC seizures were modified to only reference pediatric patients 16 years of age and older.

Conclusion:
DPMH participated in a labeling meeting on June 3, 2015, to discuss the indications, dosing, pediatric use and clinical studies subsections of Spritam™ (levetiracetam) labeling. DPMH also participated in team meetings and assisted the Division in preparing paperwork for Pediatric Review Committee (PeRC) meeting. PeRC met on June 10, 2015, and noted that there are ongoing discussions within the Agency as to whether the product triggers PREA, but agreed that under the requirements established under PREA, the product had been fully assessed for the intended populations and the plan for partial waivers was appropriate. This memorandum and labeling review reflect our recommendations provided to the Division on June 4, 2015 before labeling negotiations were finalized.

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

/s/

DONNA L SNYDER
07/01/2015

HARI C SACHS
07/01/2015
I agree with these recommendations.

LYNNE P YAO
07/02/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 19, 2015

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Cathleen Michaloski, BSN, MPH, RAC, Senior Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader, OPDP

Subject: OPDP draft full Prescribing Information (PI) and Container/Carton Label comments for SPRITAM (levetiracetam) tablets, for oral use

NDA: 207958

On November 5, 2014, DNP consulted OPDP to review the draft package insert (PI), Medication Guide, and carton and container label for the original NDA submission for SPRITAM (levetiracetam) tablets, for oral use (Spritam).

OPDP reviewed the draft substantially complete version of the PI titled "Spritam 207958 PI spon proposed 3.4.15" obtained on June 15, 2015, through the DNP Sharepoint. OPDP's comments on the draft PI are provided below. The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the draft Medication Guide under a separate cover on June 8, 2015.

Carton and Container Label:

OPDP's review of the carton label is based on the proposed carton label accessed through the following eCTD link titled "Application 207958 - Sequence 0000 - 1.14.1.1 Draft Carton and Container Labels" on June 11, 2015 (see attached). OPDP has the following comments pertaining to the proposed carton label:

The carton includes a graphic with the words [redacted] (b) (4) which could potentially be used in promotion to misleadingly suggest the product [redacted] (b) (4). OPDP recommends deleting this graphic and any other presentation such [redacted] (b) (4) as this is promotional in tone. In addition, the images and graphic makes a representation about the characteristic of the drug that denotes a benefit. Such presentations imply a benefit of the product that requires the presentation of the indication of the product and risk information on the carton. [redacted] (b) (4)

If you have any questions, please contact Aline Moukhtara (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

46 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ALINE M MOUKHTARA
06/19/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 8, 2015
To:	Billy Dunn, M.D. Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, MSN, FNP-BC, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Mathilda Fienkeng, PharmD, Team Leader **Office of Prescription Drug Promotion (OPDP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Aline M. Moukhtara, RN, MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SPRITAM (levetiracetam)
Dosage Form and Route:	Tablets for Oral Use
Application Type/Number:	NDA 207958
Applicant:	Aprecia Pharmaceuticals Co. (Aprecia)

1 INTRODUCTION

On October 1, 2014, Aprecia submitted for the Agency's review an Original New Drug Application (NDA) for SPRITAM (levetiracetam) Oral (b) (4) (tablets). SPRITAM is indicated for adjunctive therapy in the treatment of:

- Partial onset seizures in patients (b) (4) of age and older with epilepsy
- Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy
- Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.

Additionally, on February 27, 2015, Aprecia submitted a Patent amendment to their NDA for SPRITAM (levetiracetam) (b) (4) Levetiracetam was originally approved on November 30, 1999.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on November 4, 2014, and November 5, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SPRITAM (levetiracetam) tablets.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA Label and Labeling review was completed on May 22, 2015.

2 MATERIAL REVIEWED

- Draft SPRITAM (levetiracetam) tablets MG received on October 1, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on May 27, 2015.
- Draft SPRITAM (levetiracetam) tablets MG received on October 1, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on May 27, 2015.
- Draft SPRITAM (levetiracetam) tablets Prescribing Information (PI) received on October 1, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on May 27, 2015.
- Draft SPRITAM (levetiracetam) tablets Prescribing Information (PI) received on October 1, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on May 27, 2015.
- Approved KEPPRA (levetiracetam) tablets comparator labeling dated March 10, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

TWANDA D SCALES
06/08/2015

ALINE M MOUKHTARA
06/08/2015

MELISSA I HULETT
06/08/2015

LASHAWN M GRIFFITHS
06/08/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 22, 2015
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 207958
Product Name and Strength:	Spritam (levetiracetam) (b) (4) 250 mg, 500 mg, 750 mg, 1000 mg
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	Aprecia Pharmaceuticals Company
Submission Date:	October 1, 2014
OSE RCM #:	2014-2257
DMEPA Primary Reviewer:	Lolita White, PharmD
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

This review responds to a request from the Division of Neurology Products (DNP) to evaluate the proposed blister labels and carton labeling, Prescribing Information (PI) and Medication Guide (MG) for Spritam (levetiracetam) (b) (4) for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (n/a)
Previous DMEPA Reviews	C (n/a)
Human Factors Study	D (n/a)
ISMP Newsletters	E (n/a)
Other	F (n/a)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the submitted carton labeling, blister labels, medication guide and prescriber information (PI) and identified areas of needed improvement.

The carton labeling trade dress contains colors that overlap with the colors used for expressions of strength and the individual strengths can be better differentiated. The proposed proprietary name, Spritam, is printed in blue while the trademark graphic is predominantly orange. The color scheme of the carton is predominantly blue and white. To differentiate the strengths, there are additional graphic designs with blue being the base color and then an additional swipe of color that corresponds with the text color of each strength statement. (b) (4)

We note that the 1000 mg (b) (4) and 250 mg (blue) colors overlap with the trade dress which minimizes the predominance of the strength designations. Additionally, the colors blue

and purple are very close in shade on the (b) (4) 250 mg carton. To make the strengths more readily distinguishable, we recommend using colors for the strength statements that are distinct from the other strengths. Furthermore, due to the prominence of orange and blue throughout the trade dress, we recommend avoiding the use of these colors as a designation of strength to decrease risk of dispensing errors.

We note that the product carton labeling does not have the finished dosage form in the recommended space. We reference the draft guidance *"Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors"* which states all carton labeling should have the finished dosage form located either in the same line as the active ingredient (established name) or directly below the active ingredient (established name). Thus, the finished dosage form should be relocated to minimize medication error. Additionally, the unit of measure, "mg", should appear in text that is the same size as the statement of strength to improve readability.

We note that as currently presented, the net quantity statement on the physician sample carton labeling can be improved upon. The presentation of the net quantity can be misinterpreted to mean one dose per sample pack and may potentially put the patient at risk for errors of overdose. Additionally the statement of strength does not state the mg dose per unit. We are concerned that a patient may think they have to consume the contents of all 6 blisters to complete a dose. Thus, we recommend the wording be revised to minimize the potential for wrong dose errors.

The blister labels (sample and commercial) contain several instructional statements including "Bend and Tear", "Bend and Peel" and "Do Not Push or Crush". We are concerned that the presence of all three statements contribute to label clutter and may cause confusion. We think the instructional statements can be re-evaluated for necessity on the blister label.

We note that each carton has an (b) (4) graphic with the words (b) (4). The image appears to be an object that (b) (4) . Furthermore, according to the Aprecia website, the (b) (4) describes a characteristic of the drug that denotes a benefit. In preliminary discussion with OPDP during our initial review, such presentations implying a benefit of the product would also require the presentation of the indication of the product and risk information on the carton. Thus, we recommend the graphic depiction (b) (4) be further evaluated by OPDP for final determination regarding display of this information on the carton labeling.

We note that the submitted PI appears to be a combined labeling for all available dosage forms of levetiracetam. This PI provides dosing instructions that are variable based on patient age, weight and indication. There are some instances where the dosing instructions are provided in mg/kg; however the dose is not obtainable using a proposed strength of Spritam. (b) (4) There is no clear delineation in the prescribing information as to which dosage form is applicable in this particular mg/kg dosing scenario (i.e. when to use the oral solid dosage form and when to use the oral solution). We are concerned that calculated doses that do not align with the available dosage forms for the proposed product could result in dose rounding, product manipulation or other methods by which to achieve the unobtainable dose. Clarification should be provided throughout the labeling. Additionally, we note that in Section 2.4 Primary Generalized Tonic-Clonic Seizures Pediatric Patients Ages 6 to < 16 Years, the last sentence states "Only whole (b) (4) should be (b) (4)." This statement is not found elsewhere in the labeling. We recommend that this statement be communicated throughout the labeling.

We note the dosage form designation of (b) (4) is not a commonly known term to the general public and is being assessed for acceptability by CMC and DNP. We are concerned that, if designated a tablet, the proposed product will be indistinguishable from the already marketed tablet, Keppra (which have overlapping strengths), in the event that only the established name and dosage form is displayed (e.g., CPOE systems, or with generic transition). If the products are not distinguishable, Spritam and Keppra are vulnerable to confusion in the prescribing, dispensing and administering phases of the medication system. In the event the products have similar PK profiles, the potential for harm associated with inadvertent wrong product error would be diminished. However, if significant differences exist between the two products, a wrong product error could potentially result in patient harm. We will defer to DNP regarding the ultimate decision of dosage form designation (i.e. (b) (4) vs tablet vs other oral dosage form) 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.

4 CONCLUSION & RECOMMENDATIONS

We have identified areas in the labels and labeling that are vulnerable to medication error and we recommend revision to help ensure safe use of the proposed product. We provide recommendations in section 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.

4.1 RECOMMENDATIONS FOR THE DIVISION

- We note that each carton has an (b) (4) graphic with (b) (4) We recommend that the inclusion of the wording (b) (4) graphic on the carton be further evaluated by OPDP.
- Throughout the Dosage and Administration sections of the Prescribing Information, consider indicating when to use the available specific dosage forms (oral solid dosage form or oral solution). We are concerned that calculated doses that do not align with the available dosage forms for the proposed product could result in dose rounding, product manipulation or other methods by which to achieve the unobtainable dose.
- Include the statement "Only whole (b) (4) should be (b) (4)" in the Highlights of Prescribing Information, the Dosage and Administration Sections and within the Medication Guide.

4.2 RECOMMENDATIONS FOR APRECIA PHARMACEUTICALS

Carton Labeling: Physician Samples Carton and Commercial Carton

- We note the use of the colors blue and orange for the carton labeling trade dress. Blue and orange are also used as font and graphic colors to denote the statements of strengths for the (b) (4) carton labeling. These colors overlap with the trade dress and decrease the prominence of the strength statement. The purple color used for the (b) (4) strength does not provide adequate differentiation from the 250 mg (blue) strength. To minimize the potential risk of dispensing errors, we recommend revision of the colors to provide adequate differentiation between strengths. We recommend that the colors used to denote the statement of strength do not overlap with the carton trade dress.
- In accordance with the draft guidance *"Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors",* relocate the designated finished dosage form to be either in the same line as the active ingredient (established name) or directly below the active ingredient (established name).
- Consider revising the text of the unit of measure, "mg", to be the same font size as the statement of strength to improve readability.
- Consider revising the statements of strength to read "XXX mg per (b) (4) to clarify the strength per unit and minimize the potential for wrong dose errors.

Blister Packs: Physician Samples and Commercial

- In accordance with the draft guidance *"Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors",* relocate the designated finished dosage form to be either in the same line as the active ingredient (established name) or directly below the active ingredient (established name).

- Consider revising the text of the unit of measure, "mg", to be the same font size as the statement of strength.
- The blister labels (sample and commercial) contain several instructional statements including "Bend and Tear", "Bend and Peel" and "Do Not Push or Crush". We are concerned that the presence of all three statements contribute to label clutter and may cause confusion. Consider removing the statement "Bend and Tear" to minimize confusion.

Physician Sample Carton Labeling only:

- Revise the net quantity statement to read: 6 (b) (4) (6 (b) (4) per blister card x 1 card)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Spritam that Aprecia Pharmaceuticals Company submitted on October 1, 2014.

Table 2. Relevant Product Information for Spritam	
Initial Approval Date	October 14, 1999
Active Ingredient	Levetiracetam
Indication	Adjunctive therapy for Partial-Onset, Myoclonic and/or Primary Generalized Tonic-Clonic seizures.
Route of Administration	Oral
Dosage Form	(b) (4)
Strength	250 mg, 500 mg, 750 mg, 1000 mg
Dose and Frequency	Variable twice daily
How Supplied	Cartons of 60 (b) (4) on unit-dose blister packages containing 6 blisters per card x 10 cards.
Storage	Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F)
Container Closure	Child-resistant blisters

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Spritam labels and labeling submitted by Aprecia on October 1, 2014.

1. Commercial Carton Labeling
2. Physician Sample Carton Labeling
3. Physician Sample Blister Label
4. Commercial Blister Label
5. Prescribing Information-no image
6. Medication Guide-no image

G.2 Label and Labeling Images

(b) (4)

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

LOLITA G WHITE
05/26/2015

DANIELLE M HARRIS
05/26/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 21, 2014

TO: Division of Neurology Products

FROM: Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 207958

The Division of Bioequivalence and GLP Compliance (DBGLPC) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSI inspected the sites listed below within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Clinical	Algorithme Pharma Inc.	1200 Beaumont Ave.Mount-Royal, Quebec, Canada H3P 3P1

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

/s/

SHILA S NKAH
11/21/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: NDA 207958

Application Type: 505 (b)(2) NDA

Name of Drug/Dosage Form: SPRITAM (levetiracetam) 250, 500, 750, 1000 mg, (b) (4) tablets

Applicant: Aprecia Pharmaceuticals, Inc.

Receipt Date: October 1, 2014

Goal Date: August 1, 2015

1. Regulatory History and Applicant's Main Proposals

This is a 505b2 application (paragraph IV certification) for SPRITAM (levetiracetam) for the proposed indications:

- Partial onset seizures in patients (b) (4) of age and older with epilepsy
- Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy
- Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy

The reference product is KEPPRA (NDA 21035), approved 1999. The applicant proposes a new formulation, an (b) (4) tablet ((b) (4) a rapidly dispersing formulation through a process called three-dimensional printing (3DP) to aid patient compliance and ease of dosing in patients with difficulty swallowing. The review clock is a standard 10 month with PDUFA goal date of August 1, 2015. The applicant has received a small business waiver (no User Fee). The applicant has a bracketed stability plan (CMC). A "Reviewers Guide" has been submitted with the application. Two clinical pharmacology studies were conducted (protocols LVA-P3-491 and 11369701). There are no new clinical studies.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Sponsor did not provide a word version of the Medication Guide

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 21, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

yes 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

yes 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

yes 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

yes 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

no 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: Several areas show too much white space (with bulleted areas in HL; needs to conform to reference drug Keppra)

yes 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

yes 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

yes 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

yes 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

yes 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

yes 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

n/a 12. All text in the BW must be **bolded**.

Comment:

n/a 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

n/a 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

n/a 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.****"*).

Comment:

Recent Major Changes (RMC) in Highlights

n/a 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

n/a 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

n/a 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

yes 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

yes 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

Selected Requirements of Prescribing Information

yes 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

yes 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

no 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment: Statement including Medication Guide needs to be added.

Revision Date in Highlights

yes 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

yes 25. The TOC should be in a two-column format.

Comment:

yes 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

n/a 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

yes 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

yes 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: There are extra periods in each subsection; these need to be removed.

yes 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

yes 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

yes 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

yes 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

n/a 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

yes 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

n/a 36. In the BW, all text should be **bolded**.

Comment:

n/a 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

yes 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

yes 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

yes 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

yes 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

yes 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

General Comment: Several "content" sections are new and not all sections correspond with RD Keppra. This is a clinical review issue.

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

/s/

CATHLEEN B MICHALOSKI
11/14/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # **207958** BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: **SPRITAM** Established/Proper Name: levetiracetam Dosage Form: (b) (4) tablet ((b) (4) Strengths: 250 mg, 500 mg, 750 mg, 1000 mg EDR Location: \\CDSESUB1\evsprod\NDA207958\207958.enx		
Applicant: Aprecia Pharmaceuticals Company Agent for Applicant (if applicable):		
Date of Application: October 1, 2014 Date of Receipt: October 1, 2014 Date clock started after UN:		
PDUFA Goal Date: August 1, 2015	Action Goal Date (if different):	
Filing Date: November 30, 2014	Date of Filing Meeting: November 13, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): • Partial onset seizures in patients (b) (4) of age and older with epilepsy • Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy • Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) X 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***		X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic

	☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 117613

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X (S)	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the	☐	☐		

submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☐	☐	X	Small business waiver

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☐ Exempt (orphan, government) X Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	X	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	X	☐	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	X	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐		☐	Para IV certification pending

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
21035	KEPPRA	NPP	Dec 16, 2014
21035	KEPPRA	PED	June 16, 2015

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric

exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*	☐	X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	X	☐	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	X	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	X	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic)

	X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	X	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	X	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☐	☐		No new clinical studies
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	X	Not a controlled substance
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X	☐		Initial iPSP agreement 12/8/13 Partial waiver
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X	☐	☐	As per reference product
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X	☐	☐	As per reference product
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☐	Pending clarification w/ applicant
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	X	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) X Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X	☐		
Is the PI submitted in PLR format?[4]	X	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X	☐	☐	Need word version of MG
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	☐	☐	
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***		☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	X	Not at this time
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** February 25, 2013 ***If yes, distribute minutes before filing meeting***	X	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** June 6, 2014 ***If yes, distribute minutes before filing meeting***	X	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	X		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES X NO ☐ YES X NO Clin pharm protocol (2 studies): 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
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	X Not Applicable
CLINICAL **Comments**: no issues at this time	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: no clinical studies; BE/BA study inspection requested 11/14/14.	☐ YES X NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the***	☐ YES Date if known: X NO ☐ To be determined

reason. For example: ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	Reason:
• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	X YES ☐ NO
BIOSTATISTICS **Comments**: no stat review needed per TL	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: review issues expected for the 74 day letter	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	X YES ☐ NO ☐ YES ☐ NO X YES pending w/ CMC ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	X Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES pending per CMC ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	X N/A ☐ YES X NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	X YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Cathleen Michaloski, Sr. RPM, DNP 796-1123 **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): Feb 27, 2015 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): TBD **Comments**: Application not in the Program; 10 month standard clock PDUFA August 1, 2015.	

REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): Review Classification: X Standard Review ☐ Priority Review
ACTIONS ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
X in draft	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

NDA 207958
FILING MEETING

DATE: November 13, 2014, 1 pm – 2 pm room 4266 WO22

NDA#: NDA 207958

PROPRIETARY NAME: SPRITAM

ESTABLISHED/PROPER NAME: levetiracetam

DOSAGE FORM/STRENGTH: 250, 500, 750, 1000 mg (b) (4) tablets ((b) (4)

APPLICANT: Aprecia Pharma., Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

Partial onset seizures in patients (b) (4) of age and older with epilepsy
Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy
Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy

BACKGROUND:

This is a 505b2 application (paragraph IV certification) for SPRITAM (levetiracetam) for the proposed indications as per above. The reference product is KEPPRA (NDA 21035), approved 1999. The applicant proposes a new formulation, an (b) (4) tablet ((b) (4) a rapidly dispersing formulation through a process called three-dimensional printing (3DP) to aid patient compliance and ease of dosing in patients with difficulty swallowing. The review clock is a standard 10 month with PDUFA goal date of August 1, 2015. The applicant has received a small business waiver (no User Fee). The applicant has a bracketed stability plan (CMC). A "Reviewers Guide" has been submitted with the application. Two clinical pharmacology studies were conducted (protocols LVA-P3-491 and 11369701). There are no new clinical studies.

Type B end of phase 2 meeting – February 25, 2013
Type B pre-NDA meeting - March 28, 2014
Initial PREA iPSP agreed – December 8, 2013
Mid-cycle Meeting – February 27, 2015
PDUFA Goal Date – August 1, 2015
Associated IND: 117613

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Cathleen Michaloski	Y

	CPMS/TL:	Norman Hershkowitz	Y
Clinical Reviewer	Ramesh Raman		

Clinical Pharmacology	Reviewer:	Bei Yu	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Not needed (Per NH)	
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	J Edward Fisher	Y
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Monsoor Khan (lead) Thomas Wong (DP) Martha Heimann (DS) Akm Khairuzzaman (manuf) Teshara Bouie (PM)	Y Y Y Y N
	TL:	Olen Stephens	N
Product Quality- Biopharmaceutics	Reviewer:	Maziar Kakhi	Y
	TL:	Elsbeth Chikhale Angelica Dorantes	Y
CMC Labeling Review	Reviewer:	Martha Heimann	Y
	TL:		
Facility Review/Inspection	Reviewer:	Vibhakar Shah	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Pending per OSE	
	TL:		
OSE/DRISK (REMS)	Reviewer:	No REMS at this time	
	TL:		

PATIENT LABELING	Reviewer:	Robin Duer (DRISK)	N

	Lolita White (Patient Labeling) Y Melinda McLawhorn (DDMAC) Y

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

/s/

CATHLEEN B MICHALOSKI
11/14/2014