Cross-Discipline Team Leader Review

Date	June 27, 2025
From	Philip H. Sheridan, MD Emily R. Freilich, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 207958/S-027
Applicant	Aprecia Pharmaceuticals, LLC
Date of Submission	June 27, 2024
PDUFA Goal Date	April 27, 2025
Proprietary Name	Spritam
Established or Proper Name	Levetiracetam
Dosage Form(s)	Tablets for oral suspension 250 mg, 500 mg, 750 mg, and 1000 mg
Applicant Proposed Indication/Population	1. Treatment of partial onset seizures in patients 4 years of age and older weighing more than 20 kg 2. Treatment of myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy 3. Treatment of primary generalized tonic clonic seizures in patients 16 years of age and older
Applicant Proposed Dosing Regimen	*Note: These dosing regimens are the same as in current labeling.* Administer Spritam tablets whole 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 • 4 years (b) (4) weighing over 40 kg: 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 • (b) (4) 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 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 the recommended dose of 1500 mg twice daily Primary generalized tonic-clonic seizures in patients 6 years of age and older weighing > 40 kg • 500 mg twice daily; increase by 500 mg twice daily every 2 weeks to the recommended dose of 1500 mg twice daily Primary generalized tonic-clonic seizures in patients 6 years of age and older weighing 20 kg to 40 kg • 250 mg twice daily; increase by 250 mg twice daily every 2 weeks to the maximum recommended dose of 750 mg twice daily

Recommendation on Regulatory Action	Approval
Recommended Indication/Population	Same as proposed indication
Recommended Dosing Regimen	Same as proposed dosing

1. Benefit-Risk Assessment

This is an efficacy supplement that is proposing enteral feeding tube as a new route of administration for Spritam (levetiracetam). The proposed new route of administration by enteral feeding tube does not change the benefit risk assessment for Spritam made at the time of its approval in 2015.

2. Background

This efficacy supplement proposes the addition of enteral feeding tubes as a new route of administration for Spritam (levetiracetam) dispersible tablets for oral suspension (NDA 207958).

This supplemental NDA relies on the results of in vitro studies described in Section 3 of this summary review.

Spritam (levetiracetam) was approved on July 31, 2015, as a 505(b)(2) application using Keppra tablets (NDA 21035) as the listed drug (LD). The LD was approved on November 30, 1999, and has a well characterized safety profile.

In Section 2.1 (Important Administration Instructions), the current approved United States Prescribing Information (USPI) for Spritam states, "SPRITAM is intended to disintegrate in the mouth when taken with a sip of liquid. As a primary method of administration, place tablet on the tongue with a dry hand, follow with a sip of liquid and swallow only after the tablet disintegrates. Do not swallow tablet(s) intact. Partial tablet(s) should not be administered. SPRITAM disintegrates in a mean time of 11 seconds (ranging from 2 to 27 seconds) in the mouth when taken with a sip of liquid. Alternately, add whole SPRITAM tablet(s) to a small volume of liquid in a cup (one tablespoon or enough to cover the medicine). Allow the tablet(s) to disperse prior to consuming the entire contents immediately. After administration of the suspension, re-suspend any residue by adding an additional small volume of liquid and swallow the full amount. No attempt should be made to administer partial quantities of the dispersed tablet(s)." The rapid disintegration of Spritam in small volumes of liquid suggests that it could be administered by enteral feeding tube as is demonstrated by the results of the in vitro testing discussed in Section 3 of this summary review. The fact that partial quantities of a dispersed tablets should not be administered indicates that Spritam is not appropriate for pediatric patients less than 4 years of age and less than 20 kg in weight as discussed in Section 10 of this summary review.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) review was written by Dr. Richard Matsuoka (primary reviewer) and Dr. Joyce Crich (secondary reviewer).

The OPQ reviewers note that the Applicant is only proposing to update the product labeling, medication guide, and carton label for Spritam Tablets to include enteral feeding tube instructions as a new route of administration and to include instructions for the optional use of an oral syringe for withdrawing the tablet dispersion from a cup for administration by mouth. Therefore, no new product quality information is provided or required, and no Chemical, Manufacturing, and Control (CMC) changes are proposed to the product labeling.

The OPQ reviewers explain that that, in support of these proposed additions to labeling, the Applicant has submitted two reports which document in vitro studies conducted in accordance with the Agency's Guidance for Industry, *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations* (June 2021).

The first report, "Sedimentation Volume and Re-dispersibility of Spritam Tablets," presents the results from testing assessing the sedimentation potential and the re-dispersibility potential of the 250 mg and 1000 mg strength Spritam Tablets (the lowest and highest strength tablets marketed).

After their review of these results from the first report, the OPQ reviewers concurred with the Applicant's conclusions that:

- The sedimentation volumes were 0.6 mL for the 250 mg strength tablet and 1.6 mL for the 1000 mg strength tablet when dispersed in 5 mL of water.
- The contents of the syringes containing the dispersed 250 mg strength and 1000 mg strength tablets were fully redispersed after a holding/soaking time of 3.5 hours with minimal shaking. The OPQ reviewers noted that the rapid dispersion time of Spritam tablets in 5 ml of water (6 to 15 seconds), demonstrated in the tablet dispersion time study presented in the second report, supports enteral feeding tube administration without prior holding/soaking time.
- Spritam Tablets rapidly disperse in a dosing cup when treated with liquid. Therefore, the OPQ reviewers concluded that it is appropriate to use a catheter tip oral syringe to draw the tablet dispersion from the dosing cup for either feeding tube administration or administration by mouth.

The second report, "Feeding Tube Recovery Study of Spritam Tablets for Oral Suspension," presents the results from enteral feeding tube suitability testing to demonstrate that Spritam Tablets are suitable for enteral feeding tube administration when dispersed in 5 mL of water as the dispersion medium. Five tests were conducted: (1) tablet dispersion time, (2) pH of the medium, (3) assay sample recovery, (4) impurity sample, and (5) particle size distribution.

The tablet dispersion time study characterized the dispersion times for the 250 mg and 1000 mg strength tablets because these two strengths represent the lowest and highest doses (and the

smallest and largest tablets in physical size). The dispersion times of ten individual 250 mg strength tablets and ten individual 1000 mg strength tablets were determined when swirled in separate medication dosing cups using 5 mL of water. The mean dispersion time for the 250 mg strength tables in 5 mL of water was 6 seconds and the mean dispersion time for the 1000 mg strength tablets in 5 mL of water was 15 seconds.

The other four tests in the second report (pH of the medium, assay sample recovery, impurity sample, and particle size distribution) used the 1000 mg strength tablet because this strength tablet produces the highest amount of sediment and, therefore, presents the highest risk for blockage of the feeding tube. Three types of nasogastric (NG) enteral feeding tubes with an outer diameter of 10 FR and three types of gastrostomy (G) enteral feeding tubes with an outer diameter of 14 FR were evaluated.

After their review of these results from the second report, the OPQ reviewers concurred with the Applicant's conclusions that:

- The tablet dispersion time testing indicated that the rapid dispersion of Spritam tablets in 5 mL of the preferred enteral feeding tube dispersion medium (water) eliminates the need for a holding/soaking time prior to feeding tube administration.
- The pH of the dispersion medium (water) demonstrated the suitability of water as the dispersion medium for the enteral feeding tube route of administration.
- The assay sample recoveries of levetiracetam from the enteral feeding tube samples relative to the recoveries from the control samples were within the protocol criteria of (b) (4)% for all the tested enteral feeding tubes.
- Spritam impurity levels following enteral feeding tube administration met approved Spritam impurity acceptance criteria. None of the impurities exceeded the reporting threshold of (b) (4)% in the control samples or in any of the enteral feeding tube samples. No difference was found between the impurity levels of the control samples and those of the enteral feeding tube samples.
- The particle size distribution testing demonstrated that the Spritam formulation at the dispersion stage does not present a risk of tube blockage when exposed to the range of enteral feeding tubes (10 FR to 14 FR in outer diameter) tested. These particle size results further demonstrate that water is a suitable dispersion medium for enteral feeding tube administration. Enteral feeding tube clogging was observed at the enteral feeding tube outlet only if the enteral feeding tube assembly was not immediately rinsed with water. The G tubes with inflated balloons was the only configuration where clogging was observed, and this only occurred when the enteral feeding tube assembly was not immediately rinsed after administration. Therefore, it is recommended that, when using G tubes with inflated balloons, the enteral feeding tube and syringe be rinsed twice with approximately 10 mL portions of water immediately after administration to prevent clogging.
- The flush volume, consisting of two approximate 10 mL rinses, was effective at removing any remaining sediment in the various enteral feeding tubes in all the studies described in the second report.

After reviewing a response from the Applicant dated August 20, 2024, responding to an OPQ information request dated August 12, 2024, the OPQ review team determined that the Applicant's request for a categorical exclusion from the requirement to prepare an environmental assessment was acceptable.

In summary, the OPQ review team found all the results from the two reports submitted to support the proposed efficacy supplement to be acceptable.

The OPQ review team recommends approval of this supplemental NDA.

4. Nonclinical Pharmacology/Toxicology

Not applicable. A Nonclinical Pharmacology/Toxicology review was not required because the Applicant submitted no new nonclinical data to update the findings of the review written at the time of the approval of Spritam.

5. Clinical Pharmacology

Not applicable. A Clinical Pharmacology review was not required because the Applicant submitted no new clinical pharmacology data to update the findings of the review written at the time of the approval of Spritam.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Not applicable. A Clinical/Statistical Efficacy review was not required because the Applicant submitted no new efficacy data to update the previous efficacy findings discussed in the review written at the time of the approval of Spritam.

8. Safety

Not applicable. A Clinical Safety review was not required because the Applicant submitted no new safety data to update the findings of the review written at the time of the approval of Spritam.

9. Advisory Committee Meeting

There was no advisory committee for this supplemental NDA because the in vitro studies supporting enteral feeding tube administration were acceptable for review and the safety profile of Spritam is unchanged.

10. Pediatrics

Because enteral administration is a new route of administration, the Applicant submitted a new initial pediatric study plan (iPSP). Although the LD Keppra was approved in 2011 for partial onset seizures (POS) for patients one month of age or older, Spritam dispersible tablets were approved in 2015 only for patients with POS 4 years of age and older weighing more than 20 kg. This was because the LD labeling states, "Prescribe the [Keppra] oral solution for pediatric patients with body weight < 20 kg. Prescribe the oral solution or tablets for pediatric patients above 20 kg." Like the LD, Keppra tablets, Spritam dispersible tablets do not allow for weight-based dosing as required for patients less than 20 kg. These youngest patients can be appropriately dosed with Keppra oral solution. On June 10, 2015, the Pediatric Research Committee (PeRC) agreed that a partial waiver for POS in children less than 4 years of age and with a body weight less than 20 kg was appropriate. On March 25, 2025, the PeRC determined that this waiver was still appropriate.

11. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis (DMEPA) review, based on its evaluation of the proposed labeling and medication guide, provided specific recommendations to improve the clarity of the dosing instructions. These recommendations were considered in the labeling negotiations with the Applicant.

12. Labeling

Refer to the final negotiated product label. Labeling negotiations with the Applicant have been completed, and the Applicant has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS was not required for this supplemental NDA in order to ensure that the product's benefits outweigh its risks in the postmarket setting.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

There will be no postmarketing requirements and no postmarketing commitments for this supplemental NDA.

14. Recommended Comments to the Applicant

See the action letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
06/27/2025 04:27:09 PM

EMILY R FREILICH
06/27/2025 04:35:04 PM
On Behalf of DN2