SPRITAM- levetiracetam tablet, for suspension
Aprecia Pharmaceuticals, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPRITAM® safely and effectively. See full prescribing information for SPRITAM.
SPRITAM (levetiracetam) tablets, for oral suspension
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions (5.6)	03/2024

INDICATIONS AND USAGE

SPRITAM is indicated for the treatment of partial-onset seizures in patients 4 years of age and older weighing more than 20 kg (1.1)

SPRITAM is indicated for adjunctive therapy for the treatment of:
- Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy (1.2)
- Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy (1.3)

DOSAGE AND ADMINISTRATION

- SPRITAM is intended to disintegrate in the mouth when taken with a sip of liquid. Swallow only after the tablet disintegrates. Do not swallow tablet(s) intact. Partial tablet(s) should not be administered (2.1)
- 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 entire contents immediately (2.1)

Partial-Onset Seizures (monotherapy or adjunctive therapy)
- Adults/pediatric patients 4 years and older weighing over 40 kg: 500 mg twice daily; increase as needed/tolerated by 500 mg twice daily every 2 weeks to a maximum recommended dose of 1500 mg twice daily (2.2)
- Pediatric patients 4 years and older weighing 20 to 40 kg: 250 mg twice daily; increase by 250 mg twice daily every two weeks to a maximum of 750 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 6 Years of Age and Older
- Adults/pediatric patients 6 years and older weighing over 40 kg: 500 mg twice daily; increase as needed/tolerated by 500 mg twice daily every 2 weeks to a maximum recommended dose of 1500 mg twice daily (2.4)
- Pediatric patients 6 years and older weighing 20 to 40 kg: 250 mg twice daily; increase by 250 mg twice daily every 2 weeks to a maximum of 750 mg twice daily (2.4)

Adult Patients with Renal Impairment
- Dose adjustment is recommended based on creatinine clearance (2.5, 8.6)

DOSAGE FORMS AND STRENGTHS

- Tablets for oral suspension: 250 mg, 500 mg, 750 mg, and 1000 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to levetiracetam; angioedema and anaphylaxis have occurred (4, 5.4)

WARNINGS AND PRECAUTIONS

- Behavioral Abnormalities: psychotic symptoms, irritability, and aggressive behavior have been observed: Monitor for signs and symptoms (5.1)
- Suicidal Behavior and Ideation: Monitor for new or worsening depression, suicidal thoughts/behavior, and/or changes in mood or behavior (5.2)
- Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained experience on SPRITAM (5.3)
- Serious Dermatological Reactions: Discontinue SPRITAM at the first sign of rash unless clearly not drug related (5.5)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity: Discontinue if no alternative etiology (5.6)

- Coordination Difficulties: Monitor for ataxia, abnormal gait, and incoordination. Advise patients to not drive or operate machinery until they have gained experience on SPRITAM (5.7)
- Withdrawal Seizures: SPRITAM must be gradually withdrawn (5.8)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 5% more than placebo) include:

- Adults: somnolence, asthenia, infection, and dizziness (6.1)
- Pediatrics: fatigue, aggression, nasal congestion, decreased appetite, and irritability (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aprecia Pharmaceuticals, LLC at 1-844-882-7732 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Plasma levels of levetiracetam may be decreased and therefore need to be monitored closely during pregnancy; based on animal data, may cause fetal harm (5.11, 8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Partial-Onset Seizures

SPRITAM is indicated for the treatment of partial-onset seizures in patients 4 years of age and older weighing more than 20 kg.

1.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

SPRITAM is indicated as adjunctive therapy for 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 for the treatment of primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

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).

Administer SPRITAM orally, with or without food. The SPRITAM dosing regimen depends on the indication, age group, and renal function.

Patients should be instructed not to push the tablet through the foil. The foil should be peeled from the blister by bending up and lifting the peel tab around the blister seal.

2.2 Partial-Onset Seizures

The recommended dosing for monotherapy and adjunctive therapy is the same; as outlined below.

Adults and Pediatric Patients 4 Years and Older Weighing Over 40 kg:

Initiate SPRITAM with a daily dose of 1000 mg, given as twice daily dosing (500 mg twice daily). The daily dose may be increased every 2 weeks by increments of 1000 mg (500 mg twice daily) to a maximum recommended daily dose of 3000 mg (1500 mg twice daily). There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Pediatric Patients 4 years and Older Weighing 20 kg to 40 kg:

Initiate SPRITAM 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 (250 mg twice daily) to a maximum recommended daily dose of 1500 mg (750 mg twice daily).

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 (500 mg twice daily) every 2 weeks to the recommended daily dose of 3000 mg (1500 mg twice daily). The effectiveness of doses lower than 3000 mg/day has not been studied.

2.4 Primary Generalized Tonic-Clonic Seizures in Patients 6 Years of Age and Older

Adults and Pediatric Patients 6 Years and Older Weighing Over 40 kg:

Initiate SPRITAM with a daily dose of 1000 mg, given as twice daily dosing (500 mg twice daily). Increase the dosage by 1000 mg/day (500 mg twice daily) every 2 weeks to the recommended daily dose of 3000 mg (1500 mg twice daily). The effectiveness of doses lower than 3000 mg/day has not been adequately studied.

Pediatric Patients 6 years and Older Weighing 20 kg to 40 kg:

Initiate SPRITAM 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 (250 mg twice daily) to a maximum recommended daily dose of 1500 mg (750 mg twice daily).

2.5 Dosage Adjustments in Adult Patients with Renal Impairment

SPRITAM dosing must be individualized according to the patient's renal function status. Recommended dosage adjustments for adults are shown in Table 1. In order to calculate the dose recommended for patients with renal impairment, creatinine clearance adjusted for body surface area must be calculated. To do this an estimate of the patient's creatinine clearance (CLcr) in mL/min must first be calculated using the following formula:

$$CLcr = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \text{ (x 0.85 for female patients)}$$

Then CLcr is adjusted for body surface area (BSA) as follows:

$$CLcr\ (mL/min/1.73m^2) = \frac{CLcr\ (mL/min)}{BSA\ subject\ (m^2)} \times 1.73$$

Table 1: Dosing Regimen For Adult Patients With Renal Impairment

Group	Creatinine Clearance ($mL/min/1.73m^2$)	SPRITAM Dosage (mg)	Frequency
Normal	>80	500 to 1,500	Every 12 hours
Mild	50-80	500 to 1,000	Every 12 hours
Moderate	30-50	250 to 750	Every 12 hours
Severe	<30	250 to 500	Every 12 hours
ESRD patients using dialysis	—	500 to 1,000[1]	Every 24 hours[1]

[1] Following dialysis, a 250 to 500 mg supplemental dose is recommended.

2.6 Discontinuation of SPRITAM

Avoid abrupt withdrawal of SPRITAM in order to reduce the risk of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.8)].*

3 DOSAGE FORMS AND STRENGTHS

Tablet(s) for oral suspension:

- 250 mg: round, white to off-white, spearmint-flavored, marked with "•" on one side
- 500 mg: round, white to off-white, spearmint-flavored, marked with "V" on one side
- 750 mg: round, white to off-white, spearmint-flavored, marked with "E" on one side
- 1000 mg: round, white to off-white, spearmint-flavored, marked with "L" on one side

4 CONTRAINDICATIONS

SPRITAM is contraindicated in patients with a hypersensitivity to levetiracetam. Reactions have included anaphylaxis and angioedema *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Behavioral Abnormalities and Psychotic Symptoms

SPRITAM may cause behavioral abnormalities and psychotic symptoms. Patients treated with SPRITAM should be monitored for psychiatric signs and symptoms.

Behavioral abnormalities

In clinical studies, 13% of adult levetiracetam-treated patients and 38% of pediatric levetiracetam-treated patients (4 to 16 years of age), compared to 6% and 19% of adult and pediatric placebo-treated patients, respectively, experienced non-psychotic behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability,

nervousness, neurosis, and personality disorder).

A randomized double-blind, placebo-controlled study was performed to assess the neurocognitive and behavioral effects of levetiracetam as adjunctive therapy in pediatric patients (4 to 16 years of age). The results from an exploratory analysis indicated a worsening in levetiracetam-treated patients on aggressive behavior (one of eight behavior dimensions) as measured in a standardized and systematic way using a validated instrument, the Achenbach Child Behavior Checklist (CBCL/6-18).

In clinical studies in pediatric patients 1 month to < 4 years of age, irritability was reported in 12% of the levetiracetam-treated patients compared to 0% of placebo-treated patients.

In clinical studies, 1.7% of adult levetiracetam-treated patients discontinued treatment due to behavioral adverse reactions, compared to 0.2% of placebo-treated patients. The treatment dose was reduced in 0.8% of adult levetiracetam-treated patients and in 0.5% of placebo-treated patients. Overall, 11% of levetiracetam-treated pediatric patients experienced behavioral symptoms associated with discontinuation or dose reduction, compared to 6% of placebo-treated patients.

Psychotic symptoms

In clinical studies, 1% of levetiracetam-treated adult patients, 2% of levetiracetam-treated pediatric patients 4 to 16 years of age, and 17% of levetiracetam-treated pediatric patients 1 month to < 4 years of age experienced psychotic symptoms, compared to 0.2%, 2%, and 5% in the corresponding age groups treated with placebo. In the controlled study that assessed the neurocognitive and behavioral effects of levetiracetam in pediatric patients 4 to 16 years of age, 1.6% of levetiracetam-treated patients experienced paranoia, compared to 0% of placebo-treated patients. In the same study, 3.1% of levetiracetam-treated patients experienced confusional state, compared to 0% of placebo-treated patients *[see Use in Specific Populations (8.4)]*.

In clinical studies, two (0.3%) levetiracetam-treated adult patients were hospitalized and their treatment was discontinued due to psychosis. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. There was no difference between drug and placebo-treated patients in the incidence of the pediatric patients who discontinued treatment due to psychotic and non-psychotic adverse reactions.

5.2 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including SPRITAM, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond

24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing SPRITAM or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.3 Somnolence and Fatigue

SPRITAM may cause somnolence and fatigue. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on SPRITAM to gauge whether it adversely affects their ability to drive or operate machinery.

Somnolence

In controlled trials of adult patients with epilepsy experiencing partial-onset seizures, 15% of levetiracetam-treated patients reported somnolence, compared to 8% of placebo-treated patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of levetiracetam-treated patients, compared to 0% in the placebo group. About 3% of levetiracetam-treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo-treated patients. In 1.4% of levetiracetam-treated patients and 0.9% of placebo-treated patients, the dose was reduced, while 0.3% of the levetiracetam-treated patients were hospitalized due to somnolence.

Asthenia

In controlled trials of adult patients with epilepsy experiencing partial-onset seizures, 15% of levetiracetam-treated patients reported asthenia, compared to 9% of placebo-treated patients. Treatment was discontinued due to asthenia in 0.8% of levetiracetam-

treated patients as compared to 0.5% of placebo-treated patients. In 0.5% of levetiracetam-treated patients and in 0.2% of placebo-treated patients, the dose was reduced due to asthenia.

Somnolence and asthenia occurred most frequently within the first 4 weeks of treatment. In general, the incidences of somnolence and fatigue in the pediatric partial-onset seizure studies, and in pediatric and adult myoclonic and primary generalized tonic-clonic studies were comparable to those of the adult partial-onset seizure studies.

5.4 Anaphylaxis and Angioedema

SPRITAM can cause anaphylaxis or angioedema after the first dose or at any time during treatment. Signs and symptoms in cases reported in the postmarketing setting with levetiracetam have included hypotension, hives, rash, respiratory distress, and swelling of the face, lip, mouth, eye, tongue, throat, and feet. In some reported cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of anaphylaxis or angioedema, SPRITAM should be discontinued and the patient should seek immediate medical attention. SPRITAM should be discontinued permanently if a clear alternative etiology for the reaction cannot be established *[see Contraindications (4)]*.

5.5 Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both pediatric and adult patients treated with levetiracetam. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment. Recurrence of the serious skin reactions following rechallenge with levetiracetam has also been reported. SPRITAM should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

5.6 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including levetiracetam. These events can be fatal or life-threatening, particularly if diagnosis and treatment do not occur as early as possible. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. SPRITAM should be discontinued if an alternative etiology for the signs or symptoms cannot be established *[See Contraindication (4)]*.

5.7 Coordination Difficulties

SPRITAM may cause coordination difficulties.

In controlled clinical studies in adult patients with partial-onset seizures, 3.4% of adult levetiracetam-treated patients experienced coordination difficulties (reported as either ataxia, abnormal gait, or incoordination), compared to 1.6% of placebo-treated patients. A total of 0.4% of patients in controlled clinical studies discontinued levetiracetam treatment due to ataxia, compared to 0% of placebo-treated patients. In 0.7% of

levetiracetam-treated patients and in 0.2% of placebo-treated patients, the dose was reduced due to coordination difficulties, while one of the levetiracetam-treated patients was hospitalized due to worsening of pre-existing ataxia. These events occurred most frequently within the first 4 weeks of treatment.

Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on SPRITAM to gauge whether it could adversely affect their ability to drive or operate machinery.

5.8 Withdrawal Seizures

As with most antiepileptic drugs, SPRITAM should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

5.9 Hematologic Abnormalities

SPRITAM can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials with levetiracetam and included decreases in white blood cell (WBC), neutrophil, and red blood cell (RBC) counts; decreases in hemoglobin and hematocrit; and increases in eosinophil counts. Cases of agranulocytosis, pancytopenia, and thrombocytopenia have been reported in the postmarketing setting. A complete blood count is recommended in patients experiencing significant weakness, pyrexia, recurrent infections, or coagulation disorders.

<u>Partial-Onset Seizures</u>

Adults

Minor, but statistically significant decreases compared to placebo, in total mean RBC count ($0.03 \times 10^6/mm^3$), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in levetiracetam-treated patients in controlled trials.

A total of 3.2% of levetiracetam-treated and 1.8% of placebo-treated patients had at least one possibly significant ($\leq 2.8 \times 10^9$/L) decreased WBC, and 2.4% of levetiracetam-treated and 1.4% of placebo-treated patients had at least one possibly significant ($\leq 1.0 \times 10^9$/L) decreased neutrophil count. Of the levetiracetam-treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Pediatric Patients 4 Years to Less Than 16 Years of Age

Statistically significant decreases in WBC and neutrophil counts were seen in levetiracetam-treated patients as compared to placebo. The mean decreases from baseline in the levetiracetam-treated group were -0.4×10^9/L and -0.3×10^9/L, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in levetiracetam-treated patients, compared to a decrease of 4% in placebo-treated patients (statistically significant).

In a controlled trial, more levetiracetam-treated patients had a possibly clinically significant abnormally low WBC value (3% of levetiracetam-treated patients versus 0% of placebo-treated patients); however, there was no apparent difference between treatment groups with respect to neutrophil count (5% of levetiracetam-treated patients versus 4.2% of placebo-treated patients). No patient was discontinued secondary to low WBC or neutrophil counts.

In a controlled cognitive and neuropsychological safety study, 5 patients (8.6%) in the levetiracetam-treated group and two patients (6.1%) in the placebo-treated group had high eosinophil count values that were possibly clinically significant ($\geq$ 10% or $\geq 0.7 \times 10^9$/L).

5.10 Increase in Blood Pressure

In a randomized, placebo-controlled study in patients 1 month to < 4 years of age, a significantly higher risk of increased diastolic blood pressure was observed in levetiracetam-treated patients (17%), compared to the placebo-treated patients (2%). There was no overall difference in mean diastolic blood pressure between the treatment groups. This disparity between the levetiracetam and placebo treatment groups was not observed in the studies of older pediatric patients or in adults.

Monitor patients 1 month to <4 years of age for increases in diastolic blood pressure.

5.11 Seizure Control During Pregnancy

Physiological changes may gradually decrease plasma levels of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Behavioral Abnormalities and Psychotic Symptoms *[see Warnings and Precautions (5.1)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.2)]*
- Somnolence and Fatigue *[see Warnings and Precautions (5.3)]*
- Anaphylaxis and Angioedema *[see Warnings and Precautions (5.4)]*
- Serious Dermatological Reactions *[see Warnings and Precautions (5.5)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity *[see Warnings and Precautions (5.6)]*
- Coordination Difficulties *[see Warnings and Precautions (5.7)]*
- Hematologic Abnormalities *[see Warnings and Precautions (5.9)]*
- Increase in Blood Pressure *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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.

<u>Partial-Onset Seizures</u>

Adults

In controlled clinical studies in adults with partial-onset seizures *[see Clinical Studies (14.1)]*, the most common adverse reactions in patients receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, were somnolence, asthenia, infection, and dizziness. Of the most common adverse reactions in adults experiencing partial-onset seizures, asthenia, somnolence, and dizziness occurred predominantly during the first 4 weeks of treatment with levetiracetam.

Table 3 lists adverse reactions that occurred in at least 1% of adult epilepsy patients receiving levetiracetam in placebo-controlled studies and were numerically more common than in patients treated with placebo. In these studies, either levetiracetam or placebo was added to concurrent AED therapy.

Table 3: Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Studies in Adults with Partial-Onset Seizures

Adverse Reaction	Levetiracetam (N=769) %	Placebo (N=439) %
Asthenia	15	9
Somnolence	15	8
Headache	14	13
Infection	13	8
Dizziness	9	4
Pain	7	6
Pharyngitis	6	4
Depression	4	2
Nervousness	4	2
Rhinitis	4	3
Anorexia	3	2
Ataxia	3	1
Vertigo	3	1
Amnesia	2	1
Anxiety	2	1
Cough Increased	2	1
Diplopia	2	1
Emotional Lability	2	0
Hostility	2	1
Paresthesia	2	1
Sinusitis	2	1

In controlled adult clinical studies, 15% of patients receiving levetiracetam and 12% receiving placebo either discontinued or had a dose reduction as a result of an adverse reaction. Table 4 lists the most common (> 1%) adverse reactions that resulted in discontinuation or dose reduction and that occurred more frequently in levetiracetam-treated patients than in placebo-treated patients.

Table 4: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in Pooled Placebo-Controlled Studies in Adults with Partial-Onset Seizures

Adverse Reaction	Levetiracetam (N=769) %	Placebo (N=439) %
Somnolence	4	2
Dizziness	1	0

Pediatric Patients 4 Years to Less Than 16 Years of Age

The adverse reaction data presented below was obtained from a pooled analysis of two controlled clinical studies in pediatric patients 4 to less than 16 years of age with partial-onset seizures. The most common adverse reactions in pediatric patients 4 to less than 16 years of age receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, were fatigue, aggression, nasal congestion, decreased appetite, and irritability.

Table 5 lists adverse reactions from the pooled pediatric controlled studies (4 to less than 16 years of age) that occurred in at least 2% of pediatric levetiracetam-treated patients and were numerically more common than in pediatric patients treated with placebo. In these studies, either levetiracetam or placebo was added to concurrent AED

therapy.

Table 5: Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Studies in Pediatric Patients 4 to 16 Years of Age with Partial-Onset Seizures

Adverse Reaction	Levetiracetam (N=165) %	Placebo (N=131) %
Headache	19	15
Nasopharyngitis	15	12
Vomiting	15	12
Somnolence	13	9
Fatigue	11	5
Aggression	10	5
Cough	9	5
Nasal Congestion	9	2
Upper Abdominal Pain	9	8
Decreased Appetite	8	2
Abnormal Behavior	7	4
Dizziness	7	5
Irritability	7	1
Pharyngolaryngeal Pain	7	4
Diarrhea	6	2
Lethargy	6	5
Insomnia	5	3
Agitation	4	1
Anorexia	4	3
Head Injury	4	0
Altered Mood	3	1
Constipation	3	1
Contusion	3	1
Depression	3	1
Fall	3	2
Influenza	3	1
Affect Lability	2	1
Anxiety	2	1
Arthralgia	2	0
Confusional State	2	0
Conjunctivitis	2	0
Ear Pain	2	1
Gastroenteritis	2	0
Joint Sprain	2	1
Mood Swings	2	1
Neck Pain	2	1
Rhinitis	2	0
Sedation	2	1

In the controlled pooled pediatric clinical studies in patients 4 years to 16 years of age, 7% of patients receiving levetiracetam and 9% receiving placebo discontinued as a result of an adverse reaction.

Myoclonic Seizures

Although the pattern of adverse reactions in this study seems somewhat different from that seen in patients with partial-onset seizures, this is likely due to the much smaller number of patients in this study compared to partial seizure studies. The adverse reaction pattern for patients with JME is expected to be essentially the same as for patients with partial seizures.

In the controlled clinical study in patients 12 years of age and older with myoclonic seizures, *[see Clinical Studies (14.2)]*, the most common adverse reactions in patients receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, were somnolence, neck pain, and pharyngitis.

Table 6 lists adverse reactions that occurred in at least 5% of juvenile myoclonic epilepsy patients experiencing myoclonic seizures treated with levetiracetam and were numerically more common than in patients treated with placebo. In this study, either levetiracetam or placebo was added to concurrent AED therapy.

Table 6: Adverse Reactions in a Placebo-Controlled, Adjunctive Study in Patients 12 Years of Age and Older with Myoclonic Seizures

Adverse Reaction	**Levetiracetam (N=60) %**	**Placebo (N=60) %**
Somnolence	12	2
Neck pain	8	2
Pharyngitis	7	0
Depression	5	2
Influenza	5	2
Vertigo	5	3

In the placebo-controlled study, 8% of patients receiving levetiracetam and 2% receiving placebo either discontinued or had a dose reduction as a result of an adverse reaction. The adverse reactions that led to discontinuation or dose reduction and that occurred more frequently in levetiracetam-treated patients than in placebo-treated patients are presented in Table 7.

Table 7: Adverse Reactions that Resulted in Discontinuation or Dose Reduction in a Placebo-Controlled Study in Patients with Juvenile Myoclonic Epilepsy

Adverse Reaction	**Levetiracetam (N=60) %**	**Placebo (N=60) %**
Anxiety	3	2
Depressed mood	2	0
Depression	2	0
Diplopia	2	0
Hypersomnia	2	0
Insomnia	2	0
Irritability	2	0
Nervousness	2	0
Somnolence	2	0

Primary Generalized Tonic-Clonic Seizures

Although the pattern of adverse reactions in this study seems somewhat different from

that seen in patients with partial-onset seizures, this is likely due to the much smaller number of patients in this study compared to partial seizure studies. The adverse reaction pattern for patients with primary generalized tonic-clonic (PGTC) seizures is expected to be essentially the same as for patients with partial seizures.

In the controlled clinical trial in patients with PGTC seizures *[see Clinical Studies (14.3)]*, the most common adverse reaction in patients receiving levetiracetam in combination with other AEDs, for events with rates greater than placebo, was nasopharyngitis.

Table 8 lists adverse reactions that occurred in at least 5% of idiopathic generalized epilepsy patients experiencing PGTC seizures treated with levetiracetam and were numerically more common than in patients treated with placebo. In this study, either levetiracetam or placebo was added to concurrent AED therapy.

Table 8: Adverse Reactions in a Placebo-Controlled, Adjunctive Study in Patients 4 Years of Age and Older with PGTC Seizures

Adverse Reaction	**Levetiracetam (N=79) %**	**Placebo (N=84) %**
Nasopharyngitis	14	5
Fatigue	10	8
Diarrhea	8	7
Irritability	6	2
Mood swings	5	1

In the placebo-controlled study, 5% of patients receiving levetiracetam and 8% receiving placebo either discontinued or had a dose reduction during the treatment period as a result of an adverse reaction.

This study was too small to adequately characterize the adverse reactions that could be expected to result in discontinuation of treatment in this population. It is expected that the adverse reactions that would lead to discontinuation in this population would be similar to those resulting in discontinuation in other epilepsy trials (see Table 4 and Table 7).

In addition, the following adverse reactions were seen in other controlled adult studies of levetiracetam: balance disorder, disturbance in attention, eczema, memory impairment, myalgia, and blurred vision.

Comparison of Gender, Age, and Race

The overall adverse reaction profile of levetiracetam was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse reactions by age and race.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of levetiracetam. 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.

The listing is alphabetized: abnormal liver function test, acute kidney injury, agranulocytosis, anaphylaxis, angioedema, choreoathetosis, drug reaction with eosinophilia and systemic symptoms (DRESS), dyskinesia, erythema multiforme, hepatic failure, hepatitis, hyponatremia, muscular weakness, obsessive-compulsive disorders (OCD), pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), panic attack, thrombocytopenia, weight loss, and worsening of seizures

including in patients with SCN8A mutations. Alopecia has been reported with levetiracetam use; recovery was observed in majority of cases where levetiracetam was discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), including SPRITAM, during pregnancy. Encourage women who are taking SPRITAM during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry by calling 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary

Prolonged experience with levetiracetam in pregnant women has not identified a drug-associated risk of major birth defects or miscarriage, based on published literature, which includes data from pregnancy registries and reflects experience over two decades *[see Human Data]*. In animal studies, levetiracetam produced developmental toxicity (increased embryofetal and offspring mortality, increased incidences of fetal structural abnormalities, decreased embryofetal and offspring growth, neurobehavioral alterations in offspring) at doses similar to human therapeutic doses *[see Animal Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Levetiracetam blood levels may decrease during pregnancy *[see Warnings and Precautions (5.11)]*.

Physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester. Dose adjustments may be necessary to maintain clinical response.

Data

Human Data

While available studies cannot definitively establish the absence of risk, data from the published literature and pregnancy registries have not established an association with levetiracetam use during pregnancy and major birth defects or miscarriage.

Animal Data

When levetiracetam (0, 400, 1200, or 3600 mg/kg/day) was administered orally to pregnant rats during the period of organogenesis, reduced fetal weights and increased incidence of fetal skeletal variations were observed at the highest dose tested. There was no evidence of maternal toxicity. The no-effect dose for adverse effects on embryofetal developmental in rats (1200/mg/kg/day) is approximately 4 times the maximum recommended human dose (MRHD) of 3000 mg on a body surface area (mg/m^2) basis.

Oral administration of levetiracetam (0, 200, 600, or 1800 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and incidence of fetal skeletal variations at the mid and high dose and decreased fetal

weights and increased incidence of fetal malformations at the high dose, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development in rabbits (200 mg/kg/day) is approximately equivalent to the MRHD on a mg/m^2 basis.

Oral administration of levetiracetam (0, 70, 350, or 1800 mg/kg/day) to female rats throughout pregnancy and lactation led to an increased incidence of fetal skeletal variations, reduced fetal body weight, and decreased growth in offspring at the mid and high doses and increased pup mortality and neurobehavioral alterations in offspring at the highest dose tested. There was no evidence of maternal toxicity. The no-effect dose for adverse effects on pre- and postnatal development in rats (70 mg/kg/day) is less than the MRHD on a mg/m^2 basis.

Oral administration of levetiracetam to rats during the latter part of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Levetiracetam is excreted in human milk. There are no data on the effects of levetiracetam on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SPRITAM and any potential adverse effects on the breastfed infant from SPRITAM or from the underlying maternal condition.

8.4 Pediatric Use

SPRITAM is not recommended for pediatric patients that weigh 20 kg or less. The following sections describe age appropriate indications.

Partial-Onset Seizures

The safety and effectiveness of SPRITAM have been established for the treatment of partial-onset seizures in pediatric patients 4 years of age and older. 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 Pharmacology (12.3) and Clinical Studies (14.1)].*

Safety and effectiveness for the treatment of partial-onset seizures in pediatric patients below the age of 4 years have not been established.

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 *[see Warnings and Precautions (5.1)]*.

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)]*.

Safety and effectiveness as adjunctive therapy for the treatment of myoclonic seizures in pediatric patients below the age of 12 years have not been established.

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 6 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)]*.

Safety and effectiveness as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in pediatric patients below the age of 6 years have not been established.

Juvenile Animal Toxicity Data

Studies of levetiracetam in juvenile rats (dosed on postnatal days 4 through 52) and dogs (dosed from postnatal weeks 3 through 7) 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 demonstrate adverse effects on postnatal development.

8.5 Geriatric Use

There were 347 subjects in clinical studies of levetiracetam that were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of levetiracetam in these patients.

Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance *[see Clinical Pharmacology (12.3)]*. Dose adjustment is recommended for patients with renal impairment and supplemental doses should be given to patients after dialysis *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

10.1 Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

The highest known dose of levetiracetam received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses in postmarketing use.

10.2 Management of Overdose

There is no specific antidote for overdose with SPRITAM. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with SPRITAM.

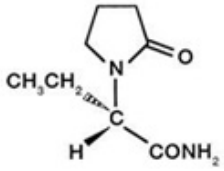
10.3 Hemodialysis

Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

11 DESCRIPTION

SPRITAM (levetiracetam) is an antiepileptic drug available as 250 mg, 500 mg, 750 mg, and 1000 mg round, white to off-white, spearmint-flavored tablets for oral suspension.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing AEDs. It has the following structural formula:



Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 mL solvent).

SPRITAM tablets for oral suspension contain 250 mg, 500 mg, 750 mg, or 1000 mg levetiracetam. Each tablet also contains the following inactive ingredients: colloidal silicon dioxide, glycerin, mannitol, microcrystalline cellulose, polysorbate 20, povidone, sucralose, butylated hydroxyanisole, and natural and artificial spearmint flavor.

SPRITAM tablets for oral suspension are unitary porous structures produced by a three-dimensional printing process that binds the powders without compression.

SPRITAM tablets for oral suspension disintegrate in a mean time of 11 seconds (ranging from 2 to 27 seconds) in the mouth, when taken with a sip of liquid, to produce small particles that may be swallowed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown.

A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle

exocytosis. Although the molecular significance of levetiracetam binding to SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiseizure activity in audiogenic seizure-prone mice. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

12.2 Pharmacodynamics

Effects on QTc Interval

The effect of levetiracetam on QTc prolongation was evaluated in a randomized, double-blind, positive-controlled (moxifloxacin 400 mg) and placebo-controlled crossover study of levetiracetam (1000 mg or 5000 mg) in 52 healthy subjects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 milliseconds. Therefore, there was no evidence of significant QTc prolongation in this study.

12.3 Pharmacokinetics

The pharmacokinetics of levetiracetam are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures.

Absorption and Distribution

Peak plasma concentrations of levetiracetam occurred in about an hour following oral administration in fasted subjects. In a crossover study in healthy volunteers, SPRITAM, administered with a sip of water, was shown to have equivalent rate and extent of absorption to levetiracetam immediate release tablets, administered with a glass of water under fasting conditions. High fat meal does not affect the extent of absorption of SPRITAM but it decreases C_{max} by 36% and delays t_{max} by 3.4 hours.

The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of levetiracetam but it decreases C_{max} by 20% and delays t_{max} by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500-5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with renal impairment [*see Dosage and Administration (2.5), Use in Specific Populations (8.6)*].

Specific Populations

Elderly

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (61-88 years of age) with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Pediatric Patients

Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (6-12 years of age) after single dose (20 mg/kg). The body weight adjusted apparent clearance of levetiracetam was approximately 40% higher than in adults.

A repeat dose pharmacokinetic study was conducted in pediatric patients (4-12 years of age) at doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. The evaluation of the pharmacokinetic profile of levetiracetam and its metabolite (ucb L057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses with a t_{max} of about 1 hour and a $t_{½}$ of 5 hours across the three dosing levels. The pharmacokinetics of levetiracetam in pediatric patients was linear between 20 to 60 mg/kg/day. The potential interaction of levetiracetam with other AEDs was also evaluated in these patients. Levetiracetam had no significant effect on the plasma concentrations of carbamazepine, valproic acid, topiramate, or lamotrigine. However, there was about a 22% increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing AED (e.g., carbamazepine).

Population pharmacokinetic analysis showed that body weight was significantly correlated to the clearance of levetiracetam in pediatric patients; clearance increased with an increase in body weight.

Pediatric Patients with Obesity

A population PK analysis of levetiracetam was conducted in 164 obese and non-obese pediatric patients 2 to <18 years of age with median (range) weight 39.2 (11.3-134) kg to evaluate the potential impact of obesity on plasma levetiracetam exposures. Obesity was defined as BMI ≥95th percentile for age and sex based on CDC 2000 growth chart recommendations. Simulations were conducted for obese and non-obese pediatric patients ages 4 to <16 years.

- When the recommended tablet dose is administered to pediatric patients weighing < 40 kg, obese pediatric patients have 27% higher median $C_{max,ss}$, and 19% higher median $C_{min,ss}$ compared to non-obese patients.
- When the recommended tablet dose is administered to pediatric patients weighing ≥ 40 kg, obese pediatric patients have 10-11% lower median $C_{max,ss}$ and 2% lower median $C_{min,ss}$ compared to non-obese patients.
- When the recommended oral solution dose is administered to pediatric patients across the full weight range, obese pediatric patients have 25% higher median $C_{max,ss}$ and 41% higher median $C_{min,ss}$ compared to non-obese pediatric patients.

However, differences in exposures between obese and non-obese pediatric patients are not expected to be clinically meaningful because the recommended dose titration at initiation of levetiracetam therapy would establish an appropriate dose for each individual patient.

Pregnancy

Levetiracetam levels may decrease during pregnancy *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)].*

Gender

Levetiracetam C_{max} and AUC were 20% higher in women (N=11) compared to men (N=12). However, clearances adjusted for body weight were comparable.

Race

Formal pharmacokinetic studies of the effects of race have not been conducted. Cross study comparisons involving Caucasians (N=12) and Asians (N=12), however, show that pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Renal Impairment

The disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLcr = 50-80 mL/min), 50% in the moderate group (CLcr = 30-50 mL/min), and 60% in the severe renal impairment group (CLcr < 30 mL/min). Clearance of levetiracetam is correlated with creatinine clearance.

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLcr > 80 mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure [*see Dosage and Administration (2.5)*].

Hepatic Impairment

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.

Drug Interactions

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C_{max} levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

Potential pharmacokinetic interactions of or with levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

Phenytoin

Levetiracetam (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

Valproate

Levetiracetam (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057.

Other Antiepileptic Drugs

Potential drug interactions between levetiracetam and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, and valproate) were also

assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

Effect of AEDs in Pediatric Patients

There was about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

Oral Contraceptives

Levetiracetam (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.

Digoxin

Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin

Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid

Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C^{ss}_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of levetiracetam on probenecid was not studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. Plasma exposure (AUC) at the highest dose was approximately 6 times that in humans at the maximum recommended daily human dose (MRHD) of 3000 mg. There was no evidence of carcinogenicity. In mice, oral administration of levetiracetam for 80 weeks (doses up to 960 mg/kg/day) or 2 years (doses up to 4000 mg/kg/day, lowered to 3000 mg/kg/day after 45 weeks due to intolerability) was not associated with an increase in tumors. The highest dose tested in mice for 2 years (3000 mg/kg/day) is approximately 5 times the MRHD on a body surface area (mg/m^2) basis.

Mutagenesis

Levetiracetam was negative in in vitro (Ames, chromosomal aberration in mammalian cells) and in vivo (mouse micronucleus) assays. The major human metabolite of levetiracetam (ucb L057) was negative in in vitro (Ames, mouse lymphoma) assays.

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at oral doses up to 1800 mg/kg/day, which were associated with plasma exposures (AUC) up to approximately 6 times that in humans at the MRHD.

14 CLINICAL STUDIES

The efficacy of SPRITAM is based upon bioavailability studies in healthy subjects comparing oral levetiracetam tablets to SPRITAM.

14.1 Partial-Onset Seizures

Effectiveness in Partial-Onset Seizures in Adults

The effectiveness of levetiracetam for the treatment of partial-onset seizures in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies in patients who had refractory partial-onset seizures with or without secondary generalization. The tablet formulation was used in all these studies. In these studies, 904 patients were randomized to placebo, 1000 mg, 2000 mg, or 3000 mg/day. Patients enrolled in Study 1 or Study 2 had refractory partial-onset seizures for at least two years and had taken two or more classical AEDs. Patients enrolled in Study 3 had refractory partial-onset seizures for at least 1 year and had taken one classical AED. At the time of the study, patients were taking a stable dose regimen of at least one and could take a maximum of two AEDs. During the baseline period, patients had to have experienced at least two partial-onset seizures during each 4-week period.

Study 1

Study 1 was a double-blind, placebo-controlled, parallel-group study conducted at 41 sites in the United States comparing levetiracetam 1000 mg/day (N=97), levetiracetam 3000 mg/day (N=101), and placebo (N=95) given in equally divided doses twice daily. After a prospective baseline period of 12 weeks, patients were randomized to one of the three treatment groups described above. The 18-week treatment period consisted of a 6-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant. 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 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). The results of the analysis of Study 1 are displayed in Table 9.

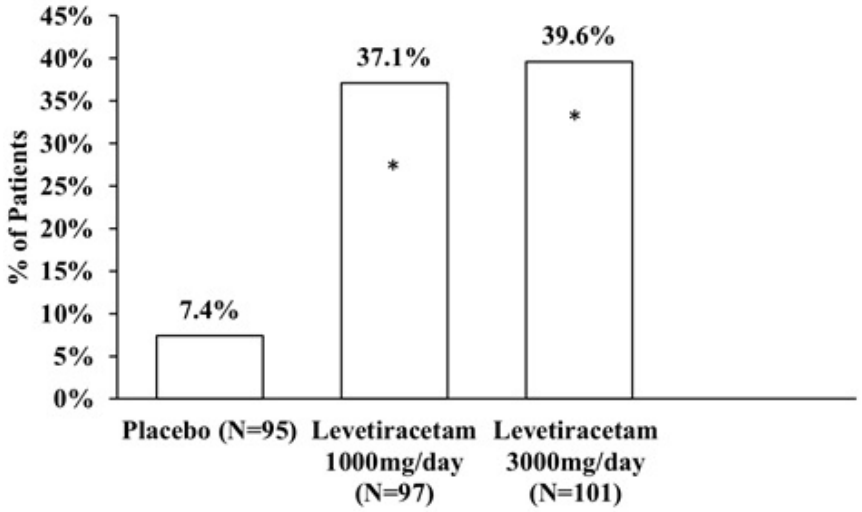
Table 9: Reduction In Mean Over Placebo In Weekly Frequency Of Partial-Onset Seizures In Study 1

	Placebo (N=95)	**Levetiracetam 1000 mg/day (N=97)**	**Levetiracetam 3000 mg/day (N=101)**
Percent reduction in partial seizure frequency over placebo	–	26%[1]	30%[1]

[1] 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 three treatment groups (x-axis) is presented in Figure 1.

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



*statistically significant versus placebo

Study 2

Study 2 was a double-blind, placebo-controlled, crossover study conducted at 62 centers in Europe comparing levetiracetam 1000 mg/day (N=106), levetiracetam 2000 mg/day (N=105), and placebo (N=111) given in equally divided doses twice daily.

The first period of the study (Period A) was designed to be analyzed as a parallel-group study. After a prospective baseline period of up to 12 weeks, patients were randomized to one of the three treatment groups described above. The 16-week treatment period consisted of the 4-week titration period followed by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant. 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 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). The results of the analysis of Period A are displayed in Table 10.

Table 10: Reduction In Mean Over Placebo In Weekly Frequency Of Partial-Onset Seizures In Study 2: Period A

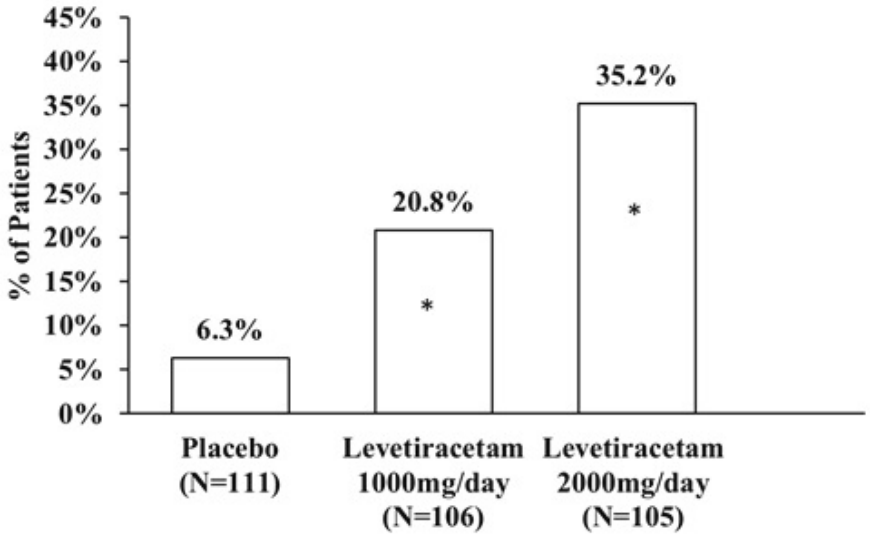
	Placebo (N=111)	**Levetiracetam 1000 mg/day (N=106)**	**Levetiracetam 2000 mg/day (N=105)**
Percent reduction in partial seizure frequency over placebo	–	17%[1]	21%[1]

[1] 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 three treatment groups (x-axis) is presented in Figure 2.

Figure 2: Responder Rate (≥ 50% Reduction From Baseline) In Study 2:

Period A



*statistically significant versus placebo

The comparison of levetiracetam 2000 mg/day to levetiracetam 1000 mg/day for responder rate was statistically significant (*P*=0.02). Analysis of the trial as a cross-over yielded similar results.

Study 3

Study 3 was a double-blind, placebo-controlled, parallel-group study conducted at 47 centers in Europe comparing levetiracetam 3000 mg/day (N=180) and placebo (N=104) in patients with refractory partial-onset seizures, with or without secondary generalization, receiving only one concomitant AED. Study drug was given in two divided doses. After a prospective baseline period of 12 weeks, patients were randomized to one of two treatment groups described above. The 16-week treatment period consisted of a 4-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED doses were held constant. The primary measure of effectiveness was a between group comparison of the percent reduction in weekly seizure frequency relative to placebo over the entire 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). Table 11 displays the results of the analysis of Study 3.

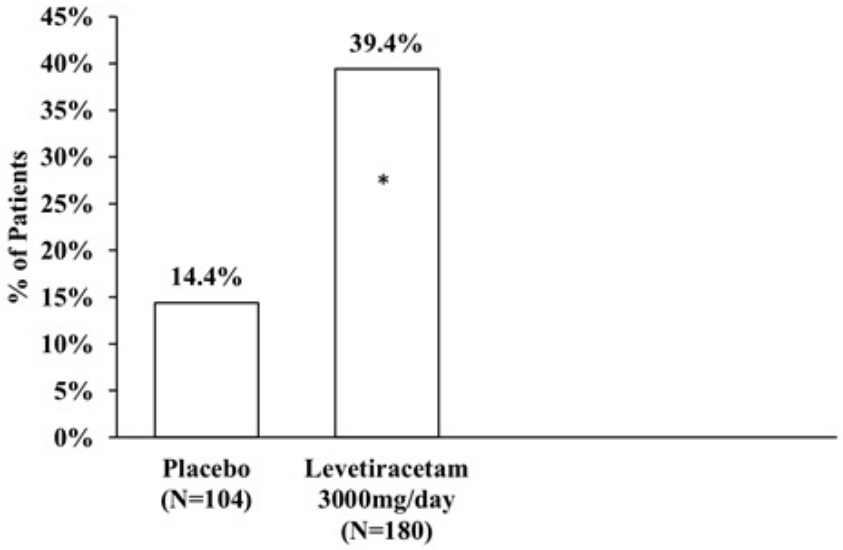
Table 11: Reduction In Mean Over Placebo In Weekly Frequency Of Partial-Onset Seizures In Study 3

	Placebo (N=104)	**Levetiracetam 3000 mg/day (N=180)**
Percent reduction in partial seizure frequency over placebo	–	23%[1]

[1] 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 Figure 3.

Figure 3: Responder Rate (≥ 50% Reduction From Baseline) In Study 3



*statistically significant versus placebo

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

The effectiveness of levetiracetam for the treatment of partial-onset seizures 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. Dosing was initiated at a dose of 20 mg/kg/day in two divided doses. During the treatment period, levetiracetam doses were adjusted in 20 mg/kg/day increments, at 2-week intervals to the target dose of 60 mg/kg/day. 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). Table 12 displays the results of this study.

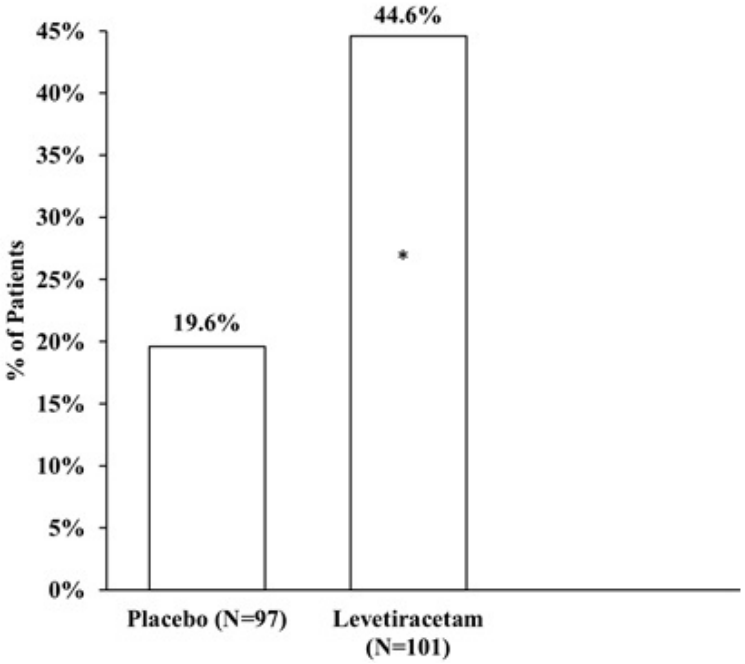
Table 12: Reduction In Mean Over Placebo In Weekly Frequency Of Partial-Onset Seizures in Study 4

	Placebo (N=97)	**Levetiracetam (N=101)**
Percent reduction in partial seizure frequency over placebo	–	27%[1]

[1] 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 Figure 4.

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



*statistically significant versus placebo

14.2 Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy

The effectiveness of levetiracetam as adjunctive therapy in patients 12 years of age and older with juvenile myoclonic epilepsy (JME) experiencing myoclonic seizures was established in one multicenter, randomized, double-blind, placebo controlled study (Study 6), conducted at 37 sites in 14 countries. Eligible patients on a stable dose of 1 antiepileptic drug (AED) experiencing one or more myoclonic seizures per day for at least 8 days during the prospective 8-week baseline period were randomized to either levetiracetam or placebo (levetiracetam N=60, placebo N=60). 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 12 weeks (evaluation period). Study drug was given in 2 divided doses.

The primary measure of effectiveness was the proportion of patients with at least 50% reduction in the number of days per week with one or more myoclonic seizures during the treatment period (titration + evaluation periods) as compared to baseline. Of the 120 patients enrolled, 113 had a diagnosis of confirmed or suspected JME. Table 13 displays the results for the 113 patients with JME in this study.

Table 13: Responder Rate (≥ 50% Reduction From Baseline) In Myoclonic Seizure Days Per Week for Patients with JME in Study 6

	Placebo (N=59)	**Levetiracetam (N=54)**
Percentage of responders	24%	60%[1]

[1] statistically significant versus placebo

14.3 Primary Generalized Tonic-Clonic Seizures

The effectiveness of levetiracetam as adjunctive therapy in patients 6 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, 6 years

of age and older, 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 for adults or a pediatric target dose of 60 mg/kg/day and treated at a stable dose of 3000 mg/day (or 60 mg/kg/day for children) 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 as summarized below in Table 14.

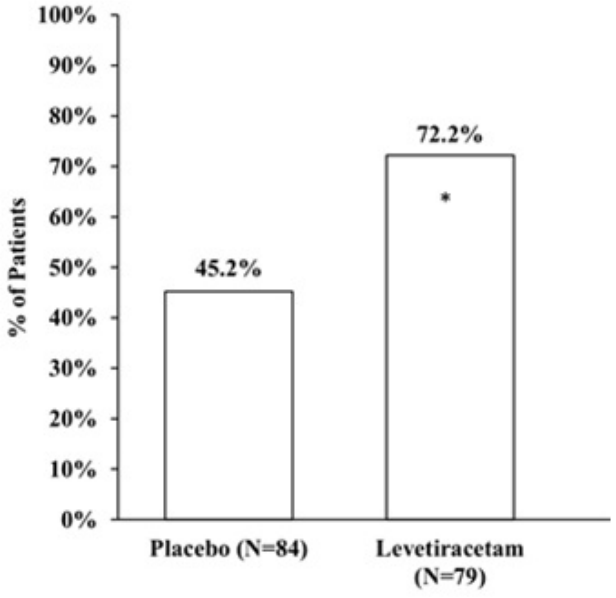
Table 14: Median Percent Reduction From Baseline In PGTC Seizure Frequency Per Week in Study 7

	Placebo (N=84)	**Levetiracetam (N=78)**
Percent reduction in PGTC seizure frequency	45%	78%[1]

[1] 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 Figure 5.

Figure 5: Responder Rate (≥ 50% Reduction From Baseline) In PGTC Seizure Frequency Per Week in Study 7



*statistically significant versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SPRITAM (levetiracetam) tablet(s) for oral suspension are supplied in child-resistant blisters as follows:

250 mg: round, white to off-white, spearmint-flavored tablets, marked with "•" on one side, 60 tablets per carton containing 6 blisters per card x 10 cards (NDC 43485-101-60); and an Institutional Use Carton of 6 unit dose Tablets x 1 Blister card (NDC 43485-101-03)

500 mg: round, white to off-white, spearmint-flavored tablets, marked with "V" on one side, 60 tablets per carton containing 6 blisters per card x 10 cards (NDC 43485-102-60); and an Institutional Use Carton of 6 unit dose Tablets x 1 Blister card (NDC 43485-102-03)

750 mg: round, white to off-white, spearmint-flavored tablets, marked with "E" on one side, 60 tablets per carton containing 6 blisters per card x 10 cards (NDC 43485-103-60); and an Institutional Use Carton of 6 unit dose Tablets x 1 Blister card (NDC 43485-103-03)

1000 mg: round, white to off-white, spearmint-flavored tablets, marked with "L" on one side, 60 tablets per carton containing 6 blisters per card x 10 cards (NDC 43485-104-60); and an Institutional Use Carton of 6 unit dose Tablets x 1 Blister card (NDC 43485-104-03)

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Psychiatric Reactions and Changes in Behavior

Advise patients that SPRITAM may cause changes in behavior (e.g. aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and psychotic symptoms [*see Warnings and Precautions (5.1)*].

Suicidal Behavior and Ideation

Counsel patients, their caregivers, and/or families that antiepileptic drugs (AEDs), including SPRITAM, may increase the risk of suicidal thoughts and behavior and advise patients to be alert for the emergence or worsening of symptoms of depression; unusual changes in mood or behavior; or suicidal thoughts, behavior, or thoughts about self-harm. Advise patients, their caregivers, and/or families to immediately report behaviors of concern to a healthcare provider [*see Warnings and Precautions (5.2)*].

Effects on Driving or Operating Machinery

Inform patients that SPRITAM may cause dizziness and somnolence. Inform patients not to drive or operate machinery until they have gained sufficient experience on SPRITAM to gauge whether it adversely affects their ability to drive or operate machinery [*see Warnings and Precautions (5.3)*]

Anaphylaxis and Angioedema

Advise patients to discontinue SPRITAM and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema [*see Warnings and Precautions (5.4)*]

Dermatological Adverse Reactions

Advise patients that serious dermatological adverse reactions have occurred in patients treated with SPRITAM and instruct them to call their physician immediately if a rash develops [*see Warnings and Precautions (5.5)*]

DRESS/Multiorgan Hypersensitivity

Instruct patients and caregivers that a fever or rash associated with signs of other organ system involvement (e.g., lymphadenopathy, hepatic dysfunction) may be drug-related and should be reported to their healthcare provider immediately. SPRITAM should be discontinued immediately if a serious hypersensitivity reaction is suspected *[see Warnings and Precautions (5.6)]*.

Withdrawal of SPRITAM

Advise patients and caregivers not to discontinue use of SPRITAM without consulting with their healthcare provider. SPRITAM should normally be gradually withdrawn to reduce the potential of increased seizure frequency and status epilepticus [*see Warnings and Precautions (5.8)]*.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during SPRITAM therapy. Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry if they become pregnant. *[see Use in Specific Populations (8.1)]*.

Administration Information

Advise patients that SPRITAM (levetiracetam) tablet(s) for oral suspension 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. Advise patients not to swallow SPRITAM intact. Partial tablets should not be administered *[see Dosage and Administration (2.1)]*.

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 attempts should be made to administer partial quantities of the dispersed tablet(s) *[see Dosage and Administration (2.1)]*.

Instruct patients to peel the foil from the blister by bending up and lifting the peel tab around the blister seal.

Manufactured by Aprecia Pharmaceuticals, LLC, Blue Ash, OH 45242 USA

Distributed by Prasco, LLC, Mason, OH 45040 USA

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Printed in the USA

Patent(s): www.aprecia.com/patents

LB-PI-0001.S

MEDICATION GUIDE
SPRITAM® (SPREE-tam)
(levetiracetam)
tablets for oral suspension

What is the most important information I should know about SPRITAM?
Like other antiepileptic drugs, SPRITAM may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it.
Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worse depression
- feeling agitated or restless
- trouble sleeping (insomnia)
- acting aggressive, being angry, or violent
- an extreme increase in activity or talking (mania)
- attempts to commit suicide
- new or worse anxiety
- panic attacks
- new or worse irritability
- acting on dangerous impulses
- other unusual changes in behavior or mood

Do not stop SPRITAM without first talking to a healthcare provider.

- Stopping SPRITAM suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus).
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- **Call your healthcare provider between visits as needed, especially if you are worried about symptoms.**

What is SPRITAM?
SPRITAM is a prescription medicine taken by mouth that used to treat partial-onset seizures in people 4 years of age and older weighing more than 20 kg (44 pounds).
SPRITAM is a prescription medicine taken by mouth that is used with other medicines to treat:

- myoclonic seizures in people 12 years of age and older with juvenile myoclonic epilepsy.
- primary generalized tonic-clonic seizures in people 6 years of age and older with certain types of generalized epilepsy.

It is not known if SPRITAM is safe or effective in children under:

- 4 years of age to treat partial-onset seizures
- 12 years of age to treat myoclonic seizures
- 6 years of age to treat primary generalized tonic-clonic seizures

SPRITAM is not recommended for children that weigh 20 kg (44 pounds) or less.

Before taking your medicine, make sure you have received the correct medicine. Compare the name above with the name on your package. Tell your pharmacist immediately if you think you have been given the wrong medicine.

Who should not take SPRITAM?

Do not take SPRITAM if you are allergic to levetiracetam.

What should I tell my healthcare provider before starting SPRITAM?

Before taking SPRITAM, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior.
- have kidney problems.
- are pregnant or planning to become pregnant. It is not known if SPRITAM will harm your unborn baby. You and your healthcare provider will have to decide if you should take SPRITAM while you are pregnant. If you become pregnant while taking SPRITAM, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334 or go to http://www.aedpregnancyregistry.org. The purpose of the registry is to collect information about the safety of SPRITAM and other antiepileptic medicine during pregnancy.
- are breastfeeding or plan to breastfeed. SPRITAM can pass into your breast milk. It is not known if the SPRITAM that passes into your breast milk can harm your baby. Talk to your doctor about the best way to feed your baby while you receive SPRITAM.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Do not start a new medicine without first talking with your healthcare provider.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I take SPRITAM?

- Take SPRITAM exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much SPRITAM to take and when to take it. SPRITAM is usually taken 2 times each day.
- Your healthcare provider may change your dose. **Do not** change your dose without talking to your healthcare provider.
- **As a main way to take SPRITAM, it is intended to disintegrate in your mouth when taken with a sip of liquid.**
- Alternately, SPRITAM may be taken by adding the whole tablet to a small volume of liquid in a cup.
  - **How to take SPRITAM with a sip of liquid:**
    - Take SPRITAM as shown on the SPRITAM carton (box).
    - Make sure your hands are dry before you remove the SPRITAM tablet(s).
    - Peel the foil away from the blister. Do not push the tablet(s) through the foil packaging.
    - Peel the foil away from the blister by bending up and lifting the peel tab around the blister seal.
    - Empty the tablet into your **dry hand**.
    - Place the SPRITAM tablet on your tongue and follow with a sip of liquid. **Let the tablet disintegrate all the way on your tongue before swallowing**.
    - SPRITAM disintegrates in an average time of 11 seconds (ranging from 2 to 27 seconds) in the mouth when taken with a sip of liquid.
  - **How to take SPRITAM with a small volume of liquid in a cup:**
    - Make sure your hands are dry before you remove the SPRITAM tablet(s).
    - Peel the foil away from the blister. Do not push the tablet through the foil

packaging.
    - Peel the foil away from the blister by bending up and lifting the peel tab around the blister seal.
    - Add whole SPRITAM tablet(s) to a small volume of liquid in a cup (1 tablespoon or enough to cover the medicine), and swirl gently.
    - Swallow right after the tablet(s) disintegrates.
    - If there is any medicine left in the cup, add a small volume of liquid to the cup, swirl gently, and swallow the liquid.
- SPRITAM can be taken with or without food.
- If you take too much SPRITAM, call your Poison Control Center at 1-800-222-1222 or go to the nearest emergency room right away.
- As shown on the SPRITAM carton (box), do not push the tablet through foil. The foil should be peeled away from the blister. Bend up and lift the peel tab, pulling open the seal around the blister.

What should I avoid while taking SPRITAM?
Do not drive, operate machinery or do other dangerous activities until you know how SPRITAM affects you. SPRITAM may make you dizzy or sleepy.

What are the possible side effects of SPRITAM?
- See "What is the most important information I should know about SPRITAM?"

SPRITAM can cause serious side effects.
Call your healthcare provider right away if you have any of these symptoms:
- mood and behavior changes such as aggression, agitation, anger, anxiety, apathy, mood swings, depression, hostility, and irritability. A few people may get psychotic symptoms such as hallucinations (seeing or hearing things that are really not there), delusions (false or strange thoughts or beliefs), and unusual behavior.
- extreme sleepiness, tiredness, and weakness.
- allergic reactions such as swelling of the face, lips, eyes, tongue, and throat, trouble swallowing or breathing, and hives.
- a skin rash. Serious skin rashes can happen after you start taking SPRITAM. There is no way to tell if a mild rash will become a serious reaction. Call your healthcare provider right away if you get a rash while taking SPRITAM.
- a serious allergic reaction that may affect your skin or other parts of your body such as your liver, kidneys, heart, or blood cells. This allergic reaction can be life-threatening and can cause death, particularly if it is not treated as early as possible. Call your healthcare provider right away if you have:
    - a skin rash
    - swelling of your face
    - dark urine
    - fever or swollen glands that do not go away
    - shortness of breath
    - yellowing of the skin or whites of the eyes
- problems with muscle coordination (problems walking and moving).

The most common side effects seen in adults who take SPRITAM include:
- sleepiness
- infection
- weakness
- dizziness

The most common side effects seen in children who take SPRITAM include the side effects above and:
- tiredness
- decreased appetite
- irritability

- acting aggressive
- nasal congestion

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of SPRITAM. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to Aprecia Pharmaceuticals, LLC at 1-844-882-7732 or FDA at 1-800-FDA-1088.

How should I store SPRITAM?

- **Store SPRITAM** at room temperature, between 59°F to 86°F (15°C to 30°C).
- **Keep SPRITAM and all medicines out of the reach of children.**

General information about the safe and effective use of SPRITAM.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SPRITAM for a condition for which it was not prescribed. Do not give SPRITAM to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about SPRITAM that is written for health professionals. You can also get information about SPRITAM at 1-844-882-7732.

What are the ingredients in SPRITAM?
Active ingredient: levetiracetam
Inactive ingredients: colloidal silicon dioxide, glycerin, mannitol, microcrystalline cellulose, polysorbate 20, povidone, sucralose, butylated hydroxyanisole, and natural and artificial spearmint flavor.

Manufactured by Aprecia Pharmaceuticals, LLC, Blue Ash, OH 45242 USA
Distributed by Prasco, LLC, Mason, OH 45040 USA
SPRITAM® is a registered trademark of Aprecia Pharmaceuticals, LLC.
Patent(s): www.aprecia.com/patents
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This Medication Guide has been approved by the US Food and Drug Administration. LB-PG-0001.P Revised: 03/2024

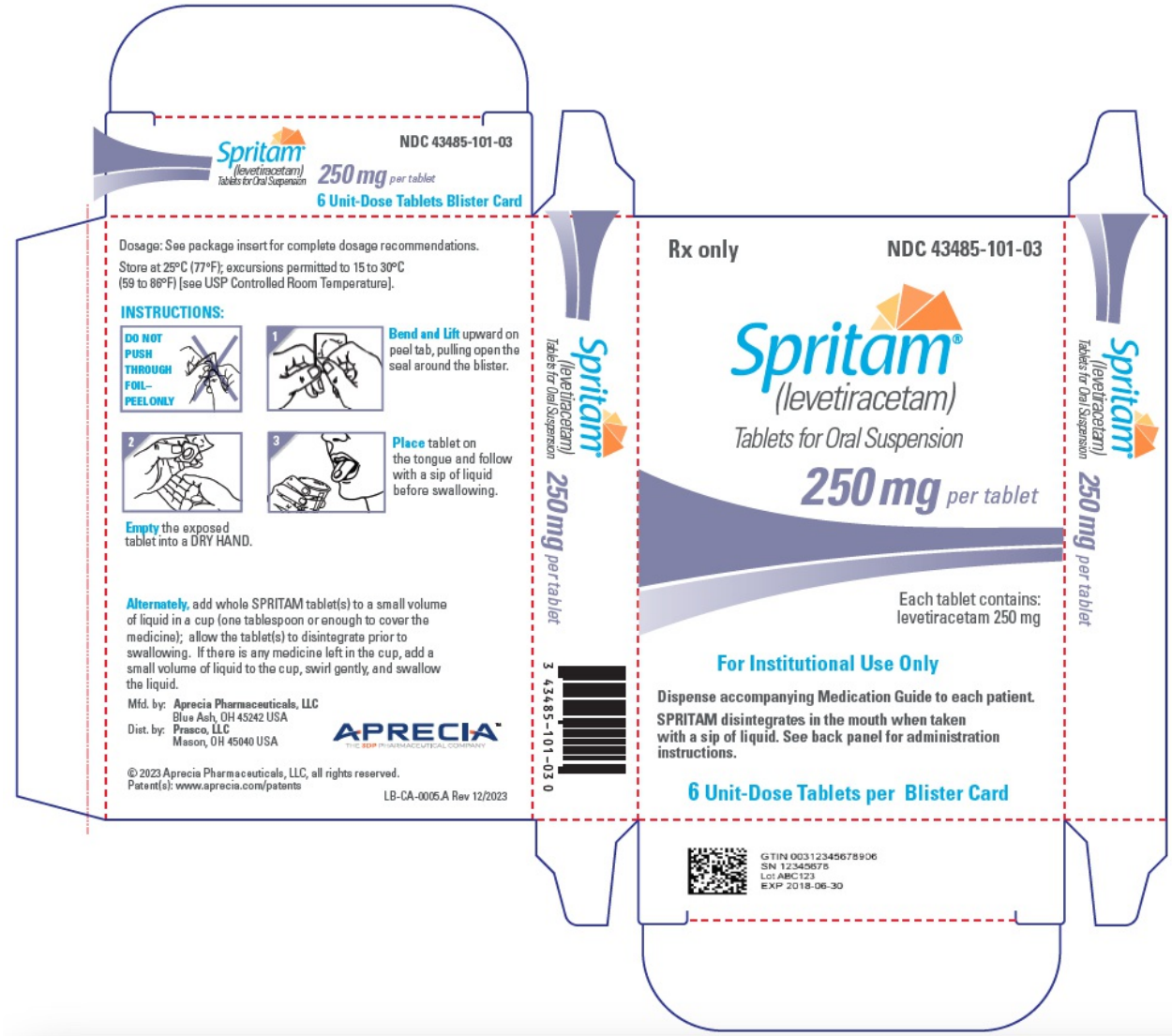
PRINCIPAL DISPLAY PANEL - NDC: 43485-101-60 - 250 mg Carton Label

PRINCIPAL DISPLAY PANEL - NDC: 43485-102-60 - 500 mg Carton Label

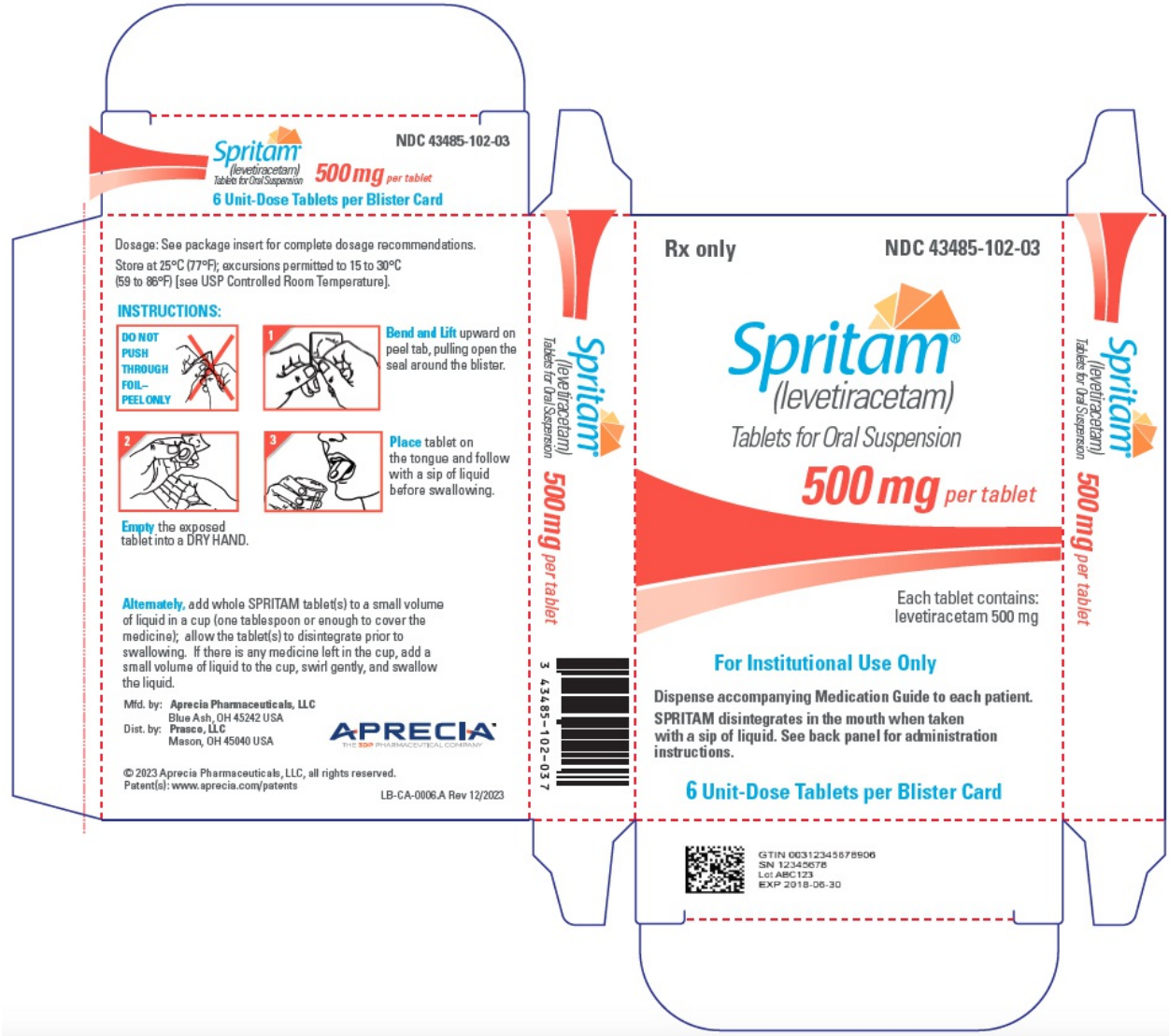
PRINCIPAL DISPLAY PANEL - NDC: 43485-103-60 - 750 mg Carton Label

PRINCIPAL DISPLAY PANEL - NDC: 43485-104-60 - 1000 mg Carton Label

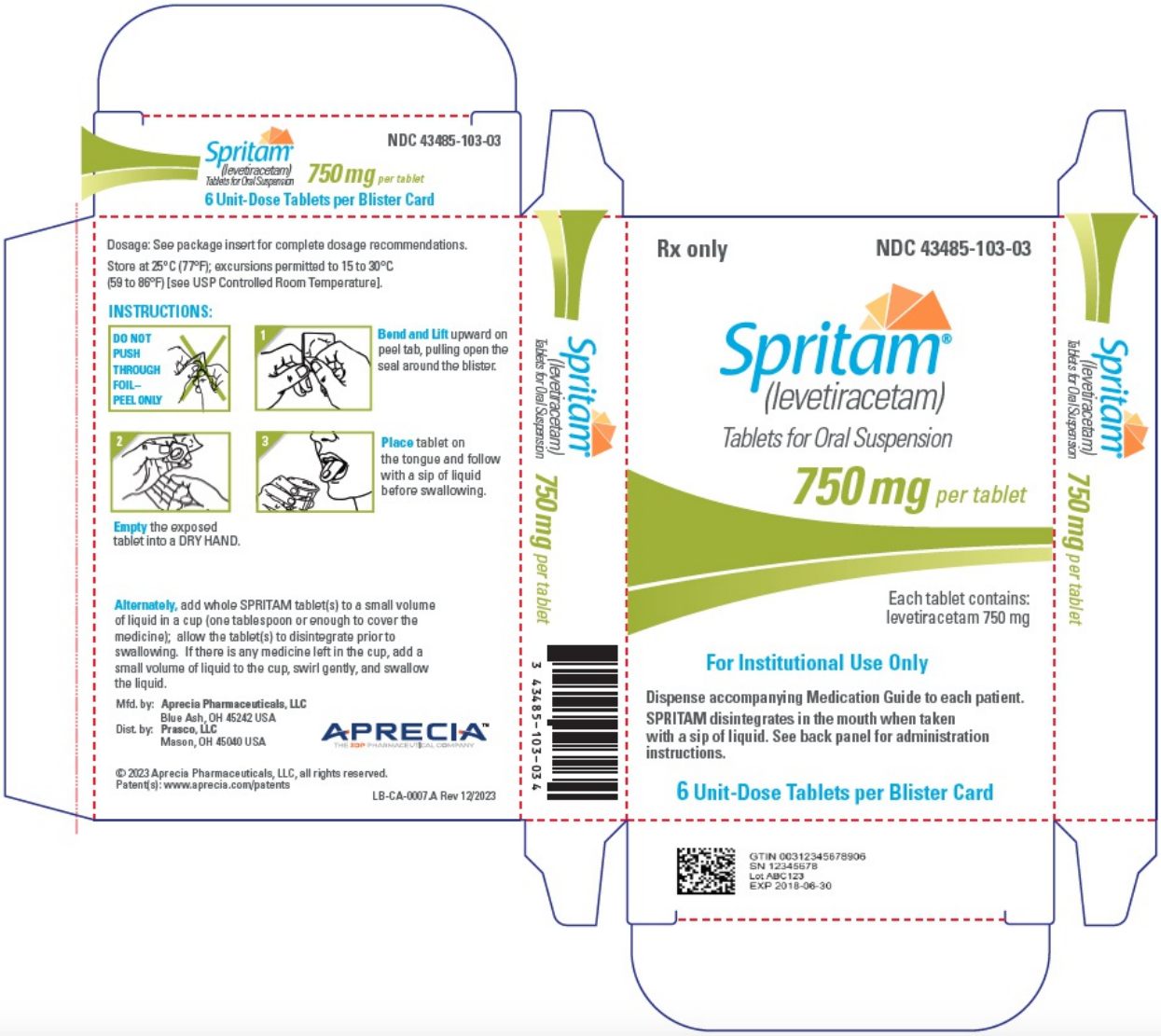
PRINCIPAL DISPLAY PANEL - NDC: 43485-101-03 - 250 mg Carton Label



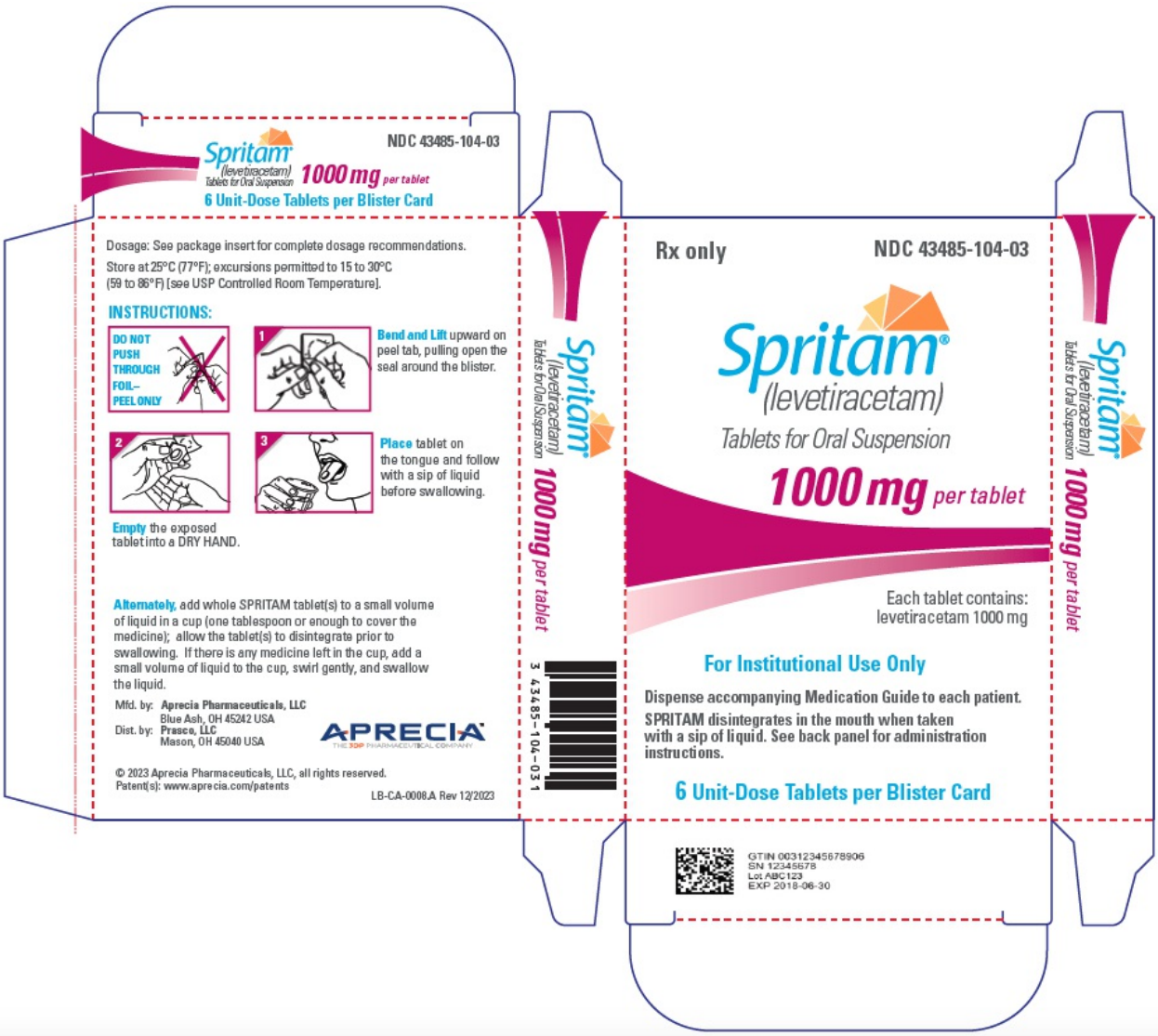
PRINCIPAL DISPLAY PANEL - NDC: 43485-102-03 - 500 mg Carton Label



PRINCIPAL DISPLAY PANEL - NDC: 43485-103-03 - 750 mg Carton Label



PRINCIPAL DISPLAY PANEL - NDC: 43485-104-03 - 1000 mg Carton Label



SPRITAM

levetiracetam tablet, for suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43485-101
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVETIRACETAM (UNII: 44YRR34555) (LEVETIRACETAM - UNII:44YRR34555)	LEVETIRACETAM	250 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GLYCERIN (UNII: PDC6A3C0OX)	
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

POLYSORBATE 20 (UNII: 7T1F30V5YH)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SPEARMINT (UNII: J7I2T6IV1N)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	13mm
Flavor	SPEARMINT	**Imprint Code**	caret;symbol;over;dot;symbol
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43485-101-60	60 in 1 CARTON	02/05/2016	
1	NDC:43485-101-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:43485-101-03	6 in 1 CARTON	06/01/2025	
2	NDC:43485-101-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207958	02/05/2016	

SPRITAM

levetiracetam tablet, for suspension

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43485-102
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVETIRACETAM (UNII: 44YRR34555) (LEVETIRACETAM - UNII:44YRR34555)	LEVETIRACETAM	500 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GLYCERIN (UNII: PDC6A3C0OX)	
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYSORBATE 20 (UNII: 7T1F30V5YH)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	

BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SPEARMINT (UNII: J7I2T6IV1N)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	17mm
Flavor	SPEARMINT	**Imprint Code**	caret;symbol;over;V
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43485-102-60	60 in 1 CARTON	02/05/2016	
1	NDC:43485-102-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:43485-102-03	6 in 1 CARTON	06/01/2025	
2	NDC:43485-102-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207958	02/05/2016	

SPRITAM

levetiracetam tablet, for suspension

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43485-103
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVETIRACETAM (UNII: 44YRR34555) (LEVETIRACETAM - UNII:44YRR34555)	LEVETIRACETAM	750 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GLYCERIN (UNII: PDC6A3C0OX)	
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYSORBATE 20 (UNII: 7T1F30V5YH)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SPEARMINT (UNII: J7I2T6IV1N)	

Product Characteristics			
Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	19mm
Flavor	SPEARMINT	**Imprint Code**	caret;symbol;over;E
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:43485-103-60	60 in 1 CARTON	02/05/2016	
1	NDC:43485-103-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:43485-103-03	6 in 1 CARTON	06/01/2025	
2	NDC:43485-103-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207958	02/05/2016	

SPRITAM

levetiracetam tablet, for suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43485-104
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVETIRACETAM (UNII: 44YRR34555) (LEVETIRACETAM - UNII:44YRR34555)	LEVETIRACETAM	1000 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
GLYCERIN (UNII: PDC6A3C0OX)	
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYSORBATE 20 (UNII: 7T1F30V5YH)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SPEARMINT (UNII: J7I2T6IV1N)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	21mm
Flavor	SPEARMINT	**Imprint Code**	caret;symbol;over;L
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43485-104-60	60 in 1 CARTON	02/05/2016	
1	NDC:43485-104-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:43485-104-03	6 in 1 CARTON	06/01/2025	
2	NDC:43485-104-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA207958	02/05/2016	

Labeler - Aprecia Pharmaceuticals, LLC (148914927)

Revised: 3/2024 Aprecia Pharmaceuticals, LLC