SUBVENITE (lamotrigine) oral suspension

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUBVENITE® safely and effectively. See full prescribing information for SUBVENITE®.

SUBVENITE (lamotrigine) oral suspension
Initial U.S. Approval: 1994

WARNING: SERIOUS SKIN RASHES
See full prescribing information for complete boxed warning.

- **Cases of life-threatening serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, associated with rash-related death have been caused by lamotrigine, the active ingredient in SUBVENITE. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include:**
  - **coadministration with valproate.**
  - **exceeding recommended initial dose of SUBVENITE.**
  - **exceeding recommended dose escalation for SUBVENITE.**
  - **beyond adolescence and the HLA-B*1502 allele. (5.1)**
- **Benign rashes are also caused by lamotrigine, the active ingredient in SUBVENITE; however, it is not possible to predict which rashes will prove to be serious or life threatening. SUBVENITE should be discontinued at the first sign of rash, unless the rash is clearly not drug related. (5.1)**

RECENT MAJOR CHANGES

Boxed Warning	08/2026
Warnings and Precautions (5.1)	08/2026
Warnings and Precautions (5.4)	08/2026

INDICATIONS AND USAGE

SUBVENITE is indicated for:
Epilepsy—adjunctive therapy in patients aged 2 years and older:
- partial-onset seizures
- primary generalized tonic-clonic (PGTC) seizures
- generalized seizures of Lennox-Gastaut syndrome.

Epilepsy—monotherapy in patients aged 16 years and older: Conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate that is a single antiepileptic drug. (1.1)

Bipolar Disorder: Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. (1.2)

Limitations of Use: Treatment of acute manic or mixed episodes is not recommended. Effectiveness of SUBVENITE in the acute treatment of mood episodes has not been established. (1.2)

DOSAGE AND ADMINISTRATION

Epilepsy:
Adjunctive therapy—See Table 1 for patients older than 12 years and Table 2 and 3 for patients aged 2 to 12 years. (2.2)
Conversion to monotherapy—See Table 4. (2.3)
Bipolar Disorder: See Table 5. (2.4)

DOSAGE FORMS AND STRENGTHS

- Oral Suspension: 10 mg/mL (3)

CONTRAINDICATIONS

Hypersensitivity to the drug or its ingredients. (Boxed Warning, 4)

WARNINGS AND PRECAUTIONS

- Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1)
- Hemophagocytic lymphohistiocytosis: Consider this diagnosis and evaluate patients immediately if they show signs or symptoms of systemic inflammation. Discontinue lamotrigine if an alternative etiology is established. (5.2)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity: Discontinue if an alternate etiology. (5.3)
- Cardiac rhythm and conduction abnormalities: Can cause death; patients with conduction abnormalities, particularly in patients with underlying cardiac disease or heart failure. (5.4)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding. (5.5)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.6)
- Aseptic meningitis: Monitor for signs of meningitis. (5.7)
- Medication errors due to product name confusion: Strongly advise patients to visually inspect their medication to ensure dose is correct. (5.8, 16, 17)

ADVERSE REACTIONS

Epilepsy: Most common adverse reactions (incidence ≥5%) in adults were nausea, dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children included vomiting, infection, fever, accidental injury, diarrhea, abdominal pain, and tremor. (6.1)

Bipolar Disorder: Most common adverse reactions (incidence ≥5%) in adults were nausea, insomnia, rhinitis, dizziness, rash, tremor, diplopia, abdominal pain, and xerostomia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GWP Pharmaceuticals, Inc. at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Valproate increases lamotrigine concentrations more than 2-fold. (7.1.2)
- Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin decrease lamotrigine concentrations by approximately 40%. (7.1.2)
- Estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7.1.2)
- Protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir decrease lamotrigine exposure by approximately 50% and 32%, respectively. (7.1.2)
- Coadministration with organic cationic transporter 2 inhibitors may increase therapeutic index is not recommended. (7.1.2)
- Drug Interactions with **OPIOIDS/Opioid Dependence**
- Pregnancy: Based on animal data may cause fetal harm. (8.1)
- Hepatic impairment: Dosage adjustments required in patients with moderate and severe liver impairment. (2.1, 8.6)
- 2 weeks (approximately 50% dose reduction per week). (2.1, 5.10)

Epilepsy:
Adjunctive therapy—See Table 1 for patients older than 12 years and Table 2 and 3 for patients aged 2 to 12 years. (2.2)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS SKIN RASHES
1 INDICATIONS AND USAGE
1.1 Epilepsy
1.2 Bipolar Disorder
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Considerations
2.2 Epilepsy—Adjunctive Therapy
2.3 Epilepsy—Conversion from Adjunctive Therapy to Monotherapy
2.4 Bipolar Disorder
2.5 Administration Instructions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Skin Rashes [see Boxed Warning]
5.2 Hemophagocytic Lymphohistiocytosis
5.3 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
5.4 Cardiac Rhythm and Conduction Abnormalities
5.5 Blood Dyscrasias
5.6 Suicidal Behavior and Ideation
5.7 Aseptic Meningitis
5.8 Potential Medication Errors
5.9 Concomitant Use with Oral Contraceptives
5.10 Withdrawal Seizures
5.11 Status Epilepticus
5.12 Addition of lamotrigine to a Multidrug Regimen that Includes Valproate
5.13 Binding in the Eye and Other Melanin-Containing Tissues
5.14 Laboratory Tests
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Other Adverse Reactions Observed in All Clinical Trials
6.3 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
10 OVERDOSAGE
10.1 Human Overdose Experience
10.2 Management of Overdose
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Epilepsy
14.2 Bipolar Disorder
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS SKIN RASHES

SUBVENITE can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.3% to 0.8% in pediatric patients (aged 2 to 17 years) and 0.08% to 0.3% in adults receiving lamotrigine. One rash-related death was reported in a prospectively followed cohort of 1,683 pediatric patients (aged 2 to 16 years) with epilepsy taking lamotrigine as adjunctive therapy. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

In addition to age, factors that may increase the risk of occurrence or the severity of rash caused by lamotrigine include (1) coadministration with valproate (see dosing recommendations, valproate sold and divalproex sodium), (2) exceeding the recommended initial dose of SUBVENITE, (3) exceeding the recommended dose escalation for SUBVENITE, or (4) the presence of the HLA-B*1502 allele. However, cases have occurred in the absence of these factors.

Nearly all cases of life-threatening rashes caused by lamotrigine have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes are also caused by lamotrigine, it is not possible to predict reliably which rashes will prove to be serious or life threatening. Accordingly, SUBVENITE should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment may prevent a rash from becoming life threatening or permanently disabling or disfiguring *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Epilepsy

Adjunctive Therapy
SUBVENITE is indicated as adjunctive therapy for the following seizure types in patients aged 2 years and older:
- partial-onset seizures.
- primary generalized tonic-clonic (PGTC) seizures.
- generalized seizures of Lennox-Gastaut syndrome.

Monotherapy
SUBVENITE is indicated for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED).

Safety and effectiveness of SUBVENITE have not been established (1) as initial monotherapy; (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate; or (3) for simultaneous conversion to monotherapy from 2 or more concomitant AEDs.

1.2 Bipolar Disorder

SUBVENITE is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy *[see Clinical Studies (14.2)]*.

Limitations of Use
Treatment of acute manic or mixed episodes is not recommended. Effectiveness of SUBVENITE in the acute treatment of mood episodes has not been established.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Considerations

Rash
There are suggestions that the risk of severe, potentially life-threatening rash may be increased by (1) coadministration of lamotrigine with valproate, (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine. However, cases have occurred in the absence of these factors *[see Boxed Warning]*. Therefore, it is important that the SUBVENITE dosing recommendations be followed closely.

The risk of nonserious rash may be increased when the recommended initial dose and/or the rate of dose escalation for SUBVENITE is exceeded and in patients with a history of allergy or rash to other AEDs. It is recommended that SUBVENITE not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine unless the benefit of restarting treatment is clear. If it is decided to restart, it is recommended that SUBVENITE be restarted on a lower dose than the original dose. If the interval since initial dose is longer than 5 half-lives, the greater consideration should be given to restarting with the initial dosing recommendations. If a patient has discontinued lamotrigine for a period of more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be followed. The half-life of lamotrigine is affected by concomitant medications *[see Clinical Pharmacology (12.3)]*.

SUBVENITE Added to Drugs Known to Induce or Inhibit Glucuronidation
Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine. Drugs that induce glucuronidation include carbamazepine, phenobarbital, phenytoin, primidone, rifampin, estrogen-containing products, including oral contraceptives, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for estrogen-containing products, including oral contraceptives, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir, see below. Lamotrigine is not known to induce or inhibit glucuronidation, see tables 1, 2, 5 to 6, and 13.

Target Plasma Levels for Patients with Epilepsy or Bipolar Disorder
Therapeutic plasma levels have not been established for lamotrigine. Dosing of SUBVENITE should be based on therapeutic response *[see Clinical Pharmacology (12.3)]*.

Women Taking Hormonal Contraceptives or Hormone Replacement Therapy
Starting SUBVENITE in Women Taking Estrogen-Containing Oral Contraceptives: Although oral contraceptives have shown to increase the lamotrigine clearance, it is not usually necessary to make adjustments to the recommended dose-escalation guidelines for SUBVENITE should be necessary, only when a clinically significant change in seizure control or an appearance or worsening of adverse reactions is observed.

If a decision is made to discontinue therapy with SUBVENITE, a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal *[see Warnings and Precautions (5.10)]*.

Discontinuing oral contraceptives, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation should prolong the half-life of lamotrigine; discontinuing *valproate* should shorten the half-life of lamotrigine.

Valproate Disorder: In the controlled clinical trials, there was no increase in the incidence, type, or severity of adverse reactions following abrupt termination of lamotrigine. In the clinical development program in adults with bipolar disorder, patients experienced seizures shortly after abrupt withdrawal of lamotrigine. Discontinuation of SUBVENITE should involve a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) unless safety concerns require a more rapid withdrawal *[see Warnings and Precautions (5.10)]*.

2.2 Epilepsy—Adjunctive Therapy

This section provides specific dosing recommendations for patients older than 12 years and patients aged 2 to 12 years. Within each of these age-groups, specific dosing recommendations are provided depending upon concomitant AEDs or other concomitant medications (see Table 1 for patients older than 12 years and Table 2 for patients aged 2 to 12 years).

Patients Older than 12 Years
Recommended dosing guidelines are summarized in Table 1.

Table 1. Escalation Regimen for SUBVENITE in Patients Older than 12 Years with Epilepsy

	In Patients TAKING Valproate*	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone†, or Valproate*	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone† and NOT TAKING Valproate*
Weeks 1 and 2	**25 mg every other day**	**25 mg every day**	**50 mg/day**
Weeks 3 and 4	**25 mg every day**	**50 mg/day**	**100 mg/day** (in 2 divided doses)
Week 5 onward to maintenance	Increase by 25 to 50 mg/day every 1 to 2 weeks.	Increase by 50 mg/day every 1 to 2 weeks.	Increase by 100 mg/day every 1 to 2 weeks.
Usual maintenance dose	**100 to 200 mg/day with valproate alone** **100 to 400 mg/day with valproate and other drugs that induce glucuronidation** (in 1 or 2 divided doses)	**225 to 375 mg/day** (in 2 divided doses)	**300 to 500 mg/day** (in 2 divided doses)

* Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.
† Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified AEDs, include estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used with AEDs that induce glucuronidation and increase clearance *[see Dosage and Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Patients Aged 2 to 12 Years
Recommended dosing guidelines are summarized in Table 2.
Lower starting doses and slower dose escalations than those used in clinical trials are recommended because of the suggestion that the risk of rash may be decreased by lower starting doses and slower dose escalations. Therefore, maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an individualized maintenance dose. Maintenance doses in patients weighing ~30 kg, regardless of age or concomitant AED, may need to be increased as much as 50%, based on clinical response.

Table 2. Escalation Regimen for SUBVENITE in Patients Aged 2 to 12 Years with Epilepsy

	In Patients TAKING Valproate*	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone†, or Valproate*	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone† and NOT TAKING Valproate*
Weeks 1 and 2	**0.15 mg/kg/day** in 1 or 2 divided doses	**0.3 mg/kg/day** in 1 or 2 divided doses	**0.6 mg/kg/day** in 2 divided doses
Weeks 3 and 4	**0.3 mg/kg/day** in 1 or 2 divided doses	**0.6 mg/kg/day** in 2 divided doses	**1.2 mg/kg/day** in 2 divided doses
Week 5 onward to maintenance	Increase by 0.15 to 0.3 mg/kg every 1 to 2 weeks.	Increase by 0.3 to 0.6 mg/kg every 1 to 2 weeks.	Increase by 0.6 to 1.2 mg/kg every 1 to 2 weeks.
Usual maintenance dose	**1 to 5 mg/kg/day** (maximum 200 mg/day in 1 or 2 divided doses)	**4.5 to 7.5 mg/kg/day** (maximum 300 mg/day in 2 divided doses)	**5 to 15 mg/kg/day** (maximum 500 mg/day in 2 divided doses)
	1 to 3 mg/kg/day with valproate alone		
Maintenance dose in patients <30 kg	May need to be increased by as much as 50%, based on clinical response.	May need to be increased by as much as 50%, based on clinical response.	May need to be increased by as much as 50%, based on clinical response.

* Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.
† Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified AEDs, include estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for estrogen-containing products, including oral contraceptives, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir, see below. Dosing recommendations for oral contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used with AEDs that induce glucuronidation and increase clearance *[see Dosage and Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Usual Adjunctive Maintenance Dose for Epilepsy
The usual maintenance doses identified in Tables 1 and 2 are derived from dosing regimens employed in the placebo-controlled adjunctive trials in which the efficacy of lamotrigine was established. In patients receiving multidrug regimens employing carbamazepine, phenytoin, phenobarbital, or primidone and without valproate, maintenance doses of adjunctive lamotrigine as high as 700 mg/day have been used. In patients receiving valproate alone, maintenance doses of adjunctive lamotrigine as high as 200 mg/day have been used. The advantage of using doses above those recommended in Tables 1 to 3 has not been established in controlled trials.

2.3 Epilepsy—Conversion from Adjunctive Therapy to Monotherapy

The goal of the transition regimen is to attempt to maintain seizure control while mitigating the risk of serious rash associated with the initiation of lamotrigine.

The recommended maintenance dose of SUBVENITE as monotherapy is 500 mg/day given in 2 divided doses.

To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations for SUBVENITE should not be exceeded *[see Boxed Warning]*.

Conversion from Adjunctive Therapy with Carbamazepine, Phenytoin, Phenobarbital, or Primidone to Monotherapy with SUBVENITE
After achieving a dose of 500 mg/day of SUBVENITE using the guidelines in Table 1, the concomitant enzyme-inducing AED should be withdrawn by 20% decrements each week over a period of at least 4 weeks. The remaining AED is maintained on optimal dosage. The dose of lamotrigine should be increased in accordance with the prescribed lamotrigine clinical trial.

Conversion from Adjunctive Therapy with Valproate to Monotherapy with SUBVENITE
The conversion regimen involves the 4 steps outlined in Table 3.

Table 3. Conversion from Adjunctive Therapy with Valproate to Monotherapy with SUBVENITE in Patients Aged 16 Years and Older with Epilepsy

	SUBVENITE	Valproate
Step 1	Achieve a dose of 300 mg/day according to guidelines in Table 1.	Maintain established stable dose.
Step 2	Maintain at 200 mg/day.	Decrease dose by decrements no greater than 500 mg/day every 1 to 2 weeks for maintenance for 1 week.
Step 3	Increase to 300 mg/day and maintain for 1 week.	Decrease dose decrements to 250 mg/day and maintain for 1 week.
Step 4	Increase by 100 mg/day every 1 to 2 weeks to reach maintenance dose of 500 mg/day.	Discontinue.

Conversion from Adjunctive Therapy with Antiepileptic Drugs other than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy with SUBVENITE
The recommended initial dose and subsequent dose escalations for SUBVENITE should be adjusted in patients receiving SUBVENITE monotherapy with SUBVENITE when AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate.

2.4 Bipolar Disorder

The goal of maintenance treatment with SUBVENITE is to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy *[see Clinical Studies (14.2)]*.

Patients taking lamotrigine for more than 16 weeks should be periodically reassessed to determine the need for maintenance treatment.

Dosing
The target dose of SUBVENITE is 200 mg/day (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate, and taking other glucuronidation inhibitors such as atazanavir/ritonavir that increase the apparent clearance of lamotrigine, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitor lopinavir/ritonavir that increase the apparent clearance of lamotrigine). In the clinical trials, doses up to 400 mg/day as monotherapy were evaluated; however, no additional benefit was seen at 400 mg/day compared with 200 mg/day *[see Clinical Studies (14.2)]*. Therefore, doses above 200 mg/day are not recommended.

Treatment with SUBVENITE is introduced, based on concurrent medications, according to the regimen outlined in Table 4. If other psychotropic medications are withdrawn following stabilization, the dose of SUBVENITE should be adjusted. In patients receiving valproate, the dose of SUBVENITE should be doubled over a 2-week period in equal weekly increments (see Table 5). In patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation, the dose of SUBVENITE should be increased over a 2-week period in equal weekly increments (see Table 5). The dose of SUBVENITE may then be further adjusted to the regimen shown (200 mg) as clinically indicated.

If other drugs are subsequently introduced, the dose of SUBVENITE may need to be adjusted. In particular, the introduction of valproate requires reduction in the dose of SUBVENITE *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of SUBVENITE should not be exceeded *[see Boxed Warning]*.

Table 4. Escalation Regimen for SUBVENITE in Adults with Bipolar Disorder

	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone*, or Valproate*	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone* and NOT TAKING Valproate*
Weeks 1 and 2	25 mg every other day	25 mg/day
Weeks 3 and 4	25 mg daily	50 mg daily
Week 5	50 mg daily	100 mg daily
Week 6	100 mg daily	200 mg daily
Week 7	100 mg daily	300 mg daily (in divided doses)
Week 8		up to 400 mg daily, in divided doses
Other	1.0	1.8
Total	2.4	4.3

* Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.
† Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified AEDs, include estrogen-containing products, including oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used with AEDs that induce glucuronidation and increase clearance *[see Dosage and Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Table 5. Dosage Adjustments to Lamotrigine in Adults with Bipolar Disorder Following Discontinuation of Psychotropic Medications

	Discontinuation of Psychotropic Drugs (excluding Valproate*, Carbamazepine, Phenytoin, Phenobarbital, or Primidone†)	After Discontinuation of Valproate*	After Discontinuation of Carbamazepine, Phenytoin, Phenobarbital, or Primidone†
	Current Dose of SUBVENITE	Current Dose of SUBVENITE	Current Dose of SUBVENITE
	100 mg/day	100 mg/day	400 mg/day
Week 1	Maintain current dose of SUBVENITE	200 mg/day	400 mg/day
Week 2	Maintain current dose of SUBVENITE	200 mg/day	300 mg/day
Week 3 onward	Maintain current dose of SUBVENITE	200 mg/day	200 mg/day

* Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.
† Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified AEDs, include estrogen-containing products, including oral contraceptives, rifampin, and the protease inhibitor lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used with AEDs that induce glucuronidation and increase clearance *[see Dosage and Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

2.5 Administration Instructions

SUBVENITE can be administered with or without food.

Use a calibrated measuring device, such as an oral dosing syringe or oral dosing cup, to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

Shake well before each use. Discard any unused portion 90 days after first opening.

3 DOSAGE FORMS AND STRENGTHS

SUBVENITE oral suspension 10 mg/mL is supplied as a pink, cherry-flavored liquid.

4 CONTRAINDICATIONS

SUBVENITE is contraindicated in patients who have demonstrated hypersensitivity (e.g., rash, angioedema, acute urticaria, extensive pruritus, mucosal ulceration) to the drug or its ingredients *[see Boxed Warning, Warnings and Precautions (5.1, 5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin Rashes *[see Boxed Warning]*

Pediatric Population
The incidence of serious rash associated with hospitalization and discontinuation of lamotrigine in a prospectively followed cohort of pediatric patients (aged 2 to 17 years) is approximately 0.3% to 0.8%. One rash-related death was reported in a prospectively followed cohort of 1,983 pediatric patients (aged 2 to 16 years) with epilepsy taking lamotrigine as adjunctive therapy. Additionally, there have been two cases of toxic epidermal necrolysis (TEN) with and without permanent sequelae and/or death in U.S. and foreign postmarketing experience.

These incidences for inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly for epilepsy, 12% (8 of 482) experienced a serious rash compared with 0.6% (6 of 952) patients not taking valproate.

Adult Population
Serious rash associated with hospitalization and discontinuation of lamotrigine occurred in 0.3% (11 of 3,348) of adult patients who received lamotrigine in premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received lamotrigine as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received lamotrigine as adjunctive therapy with other psychotropic medications. In these individuals, however, in retrospect, prodromal postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate.

Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and those associated with multiorgan hypersensitivity *[see Warnings and Precautions (5.3)]*.

Risk Factors
Concomitant Use of Valproate
The incidence for inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered lamotrigine with valproate in 3 controlled clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 2 (0.16%) of 2,398 clinical trial patients and volunteers administered lamotrigine in the absence of valproate were hospitalized for rash.

Patients with History of Allergy or Rash to Other Antiepileptic Drugs
The risk of rash may be increased in patients with a history of allergy or rash to other AEDs.

Exceeding the Recommended Initial Dose of SUBVENITE
The risk of rash is increased by both exceeding the recommended initial dose of SUBVENITE and exceeding the recommended dose escalation for SUBVENITE.

*Patients with Genetic Variant Human Leukocyte Antigen (HLA)-B*1502 Allele*
Retrospective case-control studies in patients of certain Asian ancestry (e.g., Han Chinese and Thai) suggest that the HLA-B*1502 allele is associated with an increased risk (approximately 2-3 times higher) of developing Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in patients receiving carbamazepine. The risks and benefits of therapy should be weighed when considering use of SUBVENITE in patients known to be positive for HLA-B*1502 allele. Genotyping for HLA-B*1502 may facilitate decision-making in patients from populations with high prevalence of this allele. Although the association of other genetic markers with more common forms of carbamazepine-induced SJS/TEN has been reported in Asian populations, these associations have not been universally observed. Genotyping for HLA-B*1502 is not a substitute for careful clinical vigilance and patient management. Although HLA-B*1502 positive patients are at higher risk, not all patients who carry this allele will be HLA-B*1502-negative patients of any ethnicity.

5.2 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) has occurred in pediatric and adult patients taking lamotrigine, the active ingredient in SUBVENITE, for various indications. HLH is a life-threatening condition characterized by excessive activation of lymphocytes and histiocytes associated with severe systemic inflammation. It is associated with high mortality rates if not recognized early and treated. Diagnosis of HLH is based on a combination of clinical manifestations such as prolonged fever, hepatosplenomegaly, cytopenias, high serum ferritin, hypertriglyceridemia, and liver function and coagulation abnormalities. In patients known to develop HLH, lamotrigine should be discontinued. Consider this diagnosis and evaluate patients immediately and most common adverse reactions were in association with lamotrigine during adjunctive therapy in adults and not seen at lamotrigine doses ≤ 300 mg/day in adjunctive therapy in children with partial-onset seizures or generalized seizures of Lennox-Gastaut syndrome. Most common adverse reactions observed in adjunctive therapy with multiple adverse reactions during the trial, thus, patients may be included in more than 1 category.

6.1 Clinical Trial Experience

The safety of SUBVENITE has been established from adequate and well-controlled studies that were conducted in patients with epilepsy taking lamotrigine as an adjunctive therapy and in adults with bipolar disorder *[see Clinical Studies (14.1, 14.2)]*. Below is a display of the adverse reactions of lamotrigine in these clinical trials. Adverse reactions reported in clinical trials with SUBVENITE are expected to be similar to adverse reactions with other immediate-release lamotrigine products.

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

Pharmacitis, Infection
Most Common Adverse Reactions in All Clinical Trials: Adjunctive Therapy in Adults with Epilepsy: The most common adverse reactions (≥5%) in adults with epilepsy treated with lamotrigine in placebo-controlled trials. In these trials, either lamotrigine or placebo was added to the patient's current AED therapy.

Adjunctive Therapy in Children with Epilepsy: Table 7 lists adverse reactions that occurred in adult patients with epilepsy treated with lamotrigine in placebo-controlled trials. In these trials, either lamotrigine or placebo was added to the patient's current AED therapy.

Table 6. Adverse Reactions in Pooled, Placebo-Controlled Adjunctive Trials in Adult Patients with Epilepsy*†

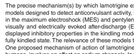
Body System/Adverse Reaction	Percent of Patients Receiving Lamotrigine (n = 711)	Percent of Patients Receiving Placebo (n = 419)
Body as a whole		
Headache	29	19
Flu syndrome	8	6
Fever	6	4
Abdominal pain	5	3
Neck pain	2	1
Reaction aggravated (seizure exacerbation)	2	1
Digestive		
Nausea	19	10
Vomiting	9	4
Diarrhea	7	3
Dyspepsia	5	2
Constipation	4	2
Anorexia	2	1
Musculoskeletal		
Arthralgia	2	0
Nervous		
Dizziness	38	13
Ataxia	18	3
Somnolence	14	7
Incoordination	6	2
Diplopia	6	2
Tremor	6	3
Depression	4	3
Anxiety	3	1
Convulsion	3	1
Irritability	2	0
Speech disorder	3	0
Concentration disturbance	2	0
Respiratory		
Rhinitis	14	9
Pharyngitis	10	5
Cough increased	8	6
Skin and appendages		
Rash	10	5
Pruritus	3	2
Special senses		
Diplopia	28	7
Blurred vision	16	5
Vision abnormality	3	1
Urogenital		
Female patients only	(n = 365)	(n = 207)
Dysmenorrhea	2	1
Vaginitis	4	1
Amenorrhea	2	1

* Adverse reactions that occurred in at least 2% of patients treated with lamotrigine and at a greater incidence than placebo.
† Patients in these adjunctive trials were receiving 1 to 3 of the concomitant AEDs carbamazepine, phenytoin, phenobarbital, or primidone in addition to valproate. Patients taking other AEDs or other concomitant medications may have reported multiple adverse reactions during the trial or at discontinuation; thus, patients may be included in more than 1 category.

In a randomized, parallel trial comparing placebo with 300 and 500 mg/day of lamotrigine, some of the more common drug-related adverse reactions were dose-related (see Table 8).

**Table 7. Adverse Reactions in Pooled, Placebo-Controlled Adjunctive Trials in Adult

cream-colored powder and has a pK_a of 5.7. Lamotrigine, USP is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural formula is:



SUBVENITE oral suspension contains 10 mg per mL lamotrigine, USP and the following inactive ingredients: carboxymethylcellulose sodium, cherry flavor, FD&C Red 40, FD&C Yellow 6, glycerin, methylparaben, polyethylene glycol, propylene glycol, purified water, saccharin sodium, silicified microcrystalline cellulose, sodium benzoate, sodium phosphate dibasic, sorbitol solution, sucralose and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known.
One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

Effect of Lamotrigine on N-Methyl-D-Aspartate-Receptor-Mediated Activity
Lamotrigine did not inhibit N-methyl-D-aspartate (NMDA)-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCMP). The IC_{50} for lamotrigine effects on NMDA-induced currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100 μM.
The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established.

12.2 Pharmacodynamics

Folate Metabolism
In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis *[see Use in Specific Populations (8.1)]*. Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Cardiac Electrophysiology
Effect of Lamotrigine: In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and slow offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. At therapeutic doses, lamotrigine did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, in patients with clinically important structural or functional heart disease or with elevated heart rates, SUBVENITE could slow ventricular conduction *[see Warnings and Precautions (5.4)]*.
Effect of Lamotrigine Metabolite: In dogs, lamotrigine is extensively metabolized to a 2-N- methyl metabolite. This metabolite causes dose-dependent prolongation of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. The *in vitro* electrophysiological effects of this metabolite have not been studied. Similar cardiovascular effects from this metabolite are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine *[see Clinical Pharmacology (12.3)]*. However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease, patients taking concomitant medications that inhibit glucuronidation).

Accumulation in Kidneys
Lamotrigine accumulated in the kidney of the male rat, causing chronic progressive nephrosis, necrosis and mineralization. These findings are attributed to α2 microglobulin, a species- and sex-specific protein that has not been detected in humans or other animal species.

Melanin Binding
Lamotrigine binds to melanin-containing tissues, e.g., in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

12.3 Pharmacokinetics

The pharmacokinetics of lamotrigine have been studied in subjects with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure. A pharmacokinetic study in healthy adult subjects under fasting conditions at a single 100 mg dose level demonstrated similar bioavailability for lamotrigine oral suspension and oral tablet.

Absorption
Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food, but the time to reach maximum plasma concentrations is delayed by 3h in presence of food *[see Dosage and Administration (2.5)]*.

Dose Proportionality
In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 mg to 400 mg. In 2 small studies (n = 7 and 8) of patients with epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and lamotrigine plasma concentrations at steady-state following doses of 50 mg to 350 mg twice daily.

Distribution
Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Protein Binding
Data from *in vitro* studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

Metabolism
Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of ^{14}C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Enzyme Induction
The effects of lamotrigine on the induction of specific families of mixed-function oxidase isozymes have not been systematically evaluated.
Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $t_{½}$ and a 37% increase in CL/F at steady state, as compared with values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation *[see Drug Interactions (7)]*. The increase in lamotrigine plasma levels will be greater if the dose of SUBVENITE is increased in the few days before or during the pill-free week. Increases in lamotrigine plasma levels could result in dose-dependent adverse reactions.
In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel component of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-pituitary-ovarian axis.
The effects of doses of lamotrigine other than 300 mg/day have not been systematically evaluated in controlled clinical trials. Studies with other female hormonal preparations (including progesterone/progesterone-containing HRT) have not been conducted.
Dosage adjustments may be necessary for women receiving estrogen-containing products, including oral contraceptive preparations *[see Dosage and Administration (2.1)]*.

Other Hormonal Contraceptives or Hormone Replacement Therapy
The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin-only pill has not shown an effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of SUBVENITE in the presence of progestogens alone will likely not be needed.

Valproate
In 18 patients with bipolar disorder on a stable regimen of 100 to 400 mg/day of lamotrigine, the lamotrigine AUC and C_{max} were reduced by approximately 10% in patients who received aripiprazole 10 to 30 mg/day for 7 days, followed by 30 mg/day for an additional 7 days. This reduction in lamotrigine exposure is not considered clinically meaningful.

Atazanavir/Ritonavir
In a study in healthy volunteers, daily doses of atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and C_{max} of lamotrigine (single 100-mg dose) by an average of 32% and 6%, respectively, and shortened the elimination half-lives by 27%. In the presence of atazanavir/ritonavir (300 mg/100 mg), the lamotrigine/metabolite ratio was increased from 0.45 to 0.71 consistent with induction of glucuronidation. The pharmacokinetics of atazanavir/ritonavir were similar in the presence of concomitant lamotrigine to the historical data of the pharmacokinetics in the absence of lamotrigine.

Bupropion
The pharmacokinetics of a 100-mg single dose of lamotrigine in healthy volunteers (n = 12) were not changed by coadministration of bupropion sustained-release formulation (150 mg twice daily) starting 11 days before lamotrigine.

Carbamazepine
Lamotrigine has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with similar dosages *[see Adverse Reactions (6.1)]*. The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide plasma concentrations decreased.
The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

Carbonate
In a trial in 21 healthy volunteers, coadministration of felbamate (1,200 mg twice daily) with lamotrigine (150 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

Folate Inhibitors
Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

Gabapentin
Based on a retrospective analysis of plasma levels in 34 subjects who received lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Lacosamide
Plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200, 400, or 600 mg/day) in placebo-controlled clinical trials in patients with partial-onset seizures.

Levetiracetam
Potential drug interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

Lithium
The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by coadministration of lamotrigine (100 mg/day) for 6 days.

Lopinavir/Ritonavir
The addition of lopinavir (400 mg twice daily)/ritonavir (100 mg twice daily) decreased the AUC, C_{max} and elimination half-life of lamotrigine by approximately 50% to 55.4% in 18 healthy subjects. The pharmacokinetics of lopinavir/ritonavir were similar with concomitant lamotrigine, compared with that in historical controls.

Olanzapine
The AUC and C_{max} of olanzapine were similar following the addition of olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 16) compared with the AUC and C_{max} in healthy male volunteers receiving olanzapine alone (n = 16).
In the same trial, the AUC and C_{max} of lamotrigine were reduced on average by 24% and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine plasma concentrations is not expected to be clinically meaningful.

Oxcarbazepine
The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy oxcarbazepine metabolite were not significantly different following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone (n = 13).
In the same trial, the AUC and C_{max} of lamotrigine were similar following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine in healthy male volunteers compared with those receiving lamotrigine alone. Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence following administration of lamotrigine and oxcarbazepine compared with lamotrigine alone or oxcarbazepine alone.

Perampanel
In a pooled analysis of data from 3 placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset seizures and PGTC seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by <10%. An effect of this magnitude is not considered to be clinically relevant.

Phenobarbital, Primidone
The addition of phenobarbital or primidone decreases lamotrigine steady-state concentrations by approximately 40%.

Phenytoin
Lamotrigine has no appreciable effect on steady-state phenytoin plasma concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 40%.

Pregabalin
Steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic interactions between lamotrigine and pregabalin.

Rifampin
In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold (AUC decreased by approximately 40%).

Risperidone
In a 14 healthy volunteers study, multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single-dose pharmacokinetics of risperidone 2 mg and its active metabolite 9-OH risperidone. Following the coadministration of risperidone 2 mg with lamotrigine, 12 of the 14 volunteers reported somnolence compared with 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

Topiramate
Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

Valproate
When lamotrigine was administered to healthy volunteers (n = 18) receiving valproate, the trough steady-state valproate plasma concentrations decreased by an average of 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing therapy did not cause a change in valproate plasma concentrations in either adult or pediatric patients in controlled clinical trials.
The addition of valproate increased lamotrigine steady-state concentrations in normal volunteers by slightly more than 2-fold. In 1 trial, maximal inhibition of lamotrigine clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as the valproate dose was further increased.

Zonisamide
In a study in 18 patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect on the pharmacokinetics of lamotrigine.

Known Inducers or Inhibitors of Glucuronidation
Drugs other than those listed above have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of lamotrigine may require adjustment based on clinical response.

Other
In vitro assessment of the inhibitory effect of lamotrigine at OCT2 demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT2 at potentially clinically relevant concentrations, with $K_{i,app}$ value of 53.8 *[See Drug Interactions (7)]*.
Results of *in vitro* experiments suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenytoin, sertraline, or trazodone.
Results of *in vitro* experiments suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6.

Specific Populations
Patients with Renal Impairment: Twelve volunteers with chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session *[see Dosage and Administration (2.1)]*.
Patients with Hepatic Impairment: The pharmacokinetics of lamotrigine following a single 100-mg dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic impairment (Child-Pugh classification system) and compared with 12 subjects without hepatic impairment. The subjects with severe hepatic impairment were without ascites (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in subjects with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment were 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared with 0.37 ± 0.09 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in subjects with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared with 33 ± 7 hours in healthy controls *[see Dosage and Administration (2.1)]*.
Pediatric Patients: The pharmacokinetics of lamotrigine following a single 2-mg/kg dose were evaluated in 2 studies in pediatric subjects (n = 29 for subjects aged 10 months to 5.9 years and n = 36 for subjects aged 5 to 11 years). Forty-three subjects received concomitant therapy with other AEDs and 12 subjects received lamotrigine as monotherapy. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 14.
Population pharmacokinetic analyses involving subjects aged 2 to 18 years demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects weighing <30 kg compared with those weighing >30 kg. Accordingly, patients weighing <30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response, as compared with subjects weighing >30 kg being administered the same AEDs *[see Dosage and Administration (2.2)]*. These analyses also revealed that, after accounting for body weight, lamotrigine clearance was not significantly influenced by age. Thus, the same weight-adjusted doses should be administered to children (irrespective of age) taking the same Concomitant AEDs which influence lamotrigine clearance in adults were found to have similar effects in children.

Table 14. Mean Pharmacokinetic Parameters in Pediatric Subjects with Epilepsy

Pediatric Study Population	Number of Subjects	T_{max} (h)	$t_{½}$ (h)	CL/F (mL/min/kg)
Ages 10 months to 5.3 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone*	10	3.0 (1.0 to 5.9)	7.7 (3.4 to 21.6)	0.42 (0.28 to 0.58)
Subjects taking antiepileptic drugs with no known effect on the apparent clearance of lamotrigine	8	5.2 (2.9 to 6.1)	19.0 (12.9 to 27.1)	1.2 (0.75 to 2.42)
Subjects taking valproate only	8	2.9 (1.0 to 6.0)	44.9 (29.5 to 52.5)	0.47 (0.23 to 0.77)
Ages 5 to 11 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone*	7	1.6 (1.0 to 3.0)	7.0 (3.8 to 9.8)	2.54 (1.35 to 5.58)
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone† plus valproate	8	3.3 (1.0 to 6.4)	19.1 (9.9 to 31.2)	0.89 (0.39 to 1.93)
Subjects taking valproate only†	3	4.5 (3.0 to 6.0)	65.8 (50.7 to 73.7)	0.24 (0.21 to 0.26)
Ages 13 to 18 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone*	11	—‡	—‡	1.3
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone† plus valproate	8	—‡	—‡	0.5
Subjects taking valproate only	4	—‡	—‡	0.3

* Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of lamotrigine. Coadministration of lopinavir/ritonavir or atazanavir/ritonavir have also been shown to increase the apparent clearance of lamotrigine *[See Drug Interactions (7)]*.
† Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of lamotrigine. Coadministration of oral contraceptives containing ethinylestradiol and lopinavir/ritonavir and atazanavir/ritonavir have also been shown to increase the apparent clearance of lamotrigine *[See Drug Interactions (7)]*.
‡ Two subjects were included in the calculation for mean T_{max}.
* Parameter not estimated.

Geriatric Patients: The pharmacokinetics of lamotrigine following a single 150-mg dose of lamotrigine were evaluated in 12 elderly volunteers between the ages of 65 and 75 years (creatinine clearance = 61 mL/min, range: 33 to 108 mL/min). The mean half-life of lamotrigine in these subjects was 31.2 hours (range: 24.1 to 43.4 hours), and the mean clearance was 0.40 mL/min/kg (range: 0.48 mL/min/kg).
Male and Female Patients: The clearance of lamotrigine is not affected by gender. However, during dose escalation of lamotrigine in 1 clinical trial in patients with epilepsy on a stable dose of valproate (n = 77), mean trough lamotrigine concentrations unadjusted for weight were 0.3 to 0.7 mcg/mL higher in females than in males.
Racial or Ethnic Groups: The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No evidence of carcinogenicity was seen in mice or rats following oral administration of lamotrigine for up to 2 years at doses up to 30 mg/kg/day and 10 to 15 mg/kg/day, respectively. The highest doses tested are less than the human dose of 400 mg/day on a body surface area (mg/m²) basis.

Mutagenesis
Lamotrigine was negative in *in vitro* gene mutation (Ames and mouse lymphoma tk) assays and in clastogenicity (*in vitro* human lymphocyte and *in vivo* rat bone marrow) assays.

Impairment of Fertility
No evidence of impaired fertility was detected in rats given oral doses of lamotrigine up to 20 mg/kg/day. The highest dose tested is less than the human dose of 400 mg/day on a mg/m² basis.

14 CLINICAL STUDIES

The efficacy of SUBVENITE for the treatment of epilepsy and bipolar disorder is based on the established effectiveness of lamotrigine oral tablet. The studies below described the effectiveness of lamotrigine oral tablet for the treatment of epilepsy and bipolar disorder. SUBVENITE (lamotrigine oral suspension) demonstrated similar bioavailability to lamotrigine oral tablet *[see Clinical Pharmacology (12.3)]*.

14.1 Epilepsy

Monotherapy with Lamotrigine in Adults with Partial-Onset Seizures Already Receiving Treatment with Carbamazepine, Phenytoin, Phenobarbital, or Primidone as Single Antiepileptic Drug
The effectiveness of monotherapy with lamotrigine was established in a multicenter, double-blind clinical trial enrolling 105 adult subjects with epilepsy who had a history of 4 to 40 partial-onset seizures during a baseline period. Complex partial-onset, and/or secondarily generalized seizures during each of 2 consecutive 4-week periods while receiving carbamazepine or phenytoin monotherapy during baseline. Lamotrigine (target dose of 500 mg/day) or valproate (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week period. Patients were then converted to monotherapy with lamotrigine or valproate during the next 4 weeks, for a total evaluation period of 12 weeks.
Trial endpoints were completion of all weeks of trial treatment or meeting an escape criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure count, (2) doubling of highest consecutive 2-week seizure frequency, (3) emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more severe than seizure types that occur during study treatment, or (4) clinically significant prolongation of generalized tonic-clonic seizures. The primary efficacy variable was the proportion of patients in each treatment group who met escape criteria.
The percentages of patients who met escape criteria were 42% (32/76) in the group receiving lamotrigine and 69% (55/80) in the valproate group. The difference in the percentage of patients meeting escape criteria was statistically significant (P= 0.0002) in favor of lamotrigine. The proportions of patients who met age, sex, or race were detected.
Adjunctive Therapy with Lamotrigine in Adults with Partial-Onset Seizures
The effectiveness of lamotrigine as adjunctive therapy (added to other AEDs) was initially established in 3 pivotal, multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial-onset seizures. The patients had a history of at least 4 partial-onset seizures per month in spite of receiving 1 or more AEDs at therapeutic concentrations and in 2 of the trials were observed on their established AED regimen during baseline(s) that varied between 8 to 12 weeks. In the third trial, patients were not observed in a prospective baseline. In patients continuing to have at least 4 seizures per month during the baseline, lamotrigine or placebo was then added to the existing therapy. In all 3 trials, change from baseline in seizure frequency was the primary measure of effectiveness. The results given below are for all partial-onset seizures in the intent-to-treat population (all patients who received at least 1 dose of treatment) in each trial, unless otherwise indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline was 6.6 per week for all patients enrolled in efficacy trials.
One trial (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and valproate was excluded. Patients were randomized to receive placebo, a target dose of 300 mg/day of lamotrigine, or a target dose of 500 mg/day of lamotrigine. The median reductions in the frequency of all partial-onset seizures relative to baseline were 8% in patients receiving placebo, 20% in patients receiving 300 mg/day of lamotrigine, and 36% in patients receiving 500 mg/day of lamotrigine. The seizure frequency reduction was statistically significant in the 500-mg/day group compared with the placebo group, but not in the 300-mg/day group.
A second trial (n = 98) was a double-blind, placebo-controlled, crossover trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose tapering) separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment periods were analyzed, the median change in seizure frequency was a 25% reduction on lamotrigine compared with placebo (P=0.001).
The third trial (n = 41) was a double-blind, placebo-controlled, crossover trial consisting of two 12-week treatment periods separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these patients received 150 mg/day of lamotrigine. The 28 other patients had a target dose of 300 mg/day of lamotrigine. The median change in seizure frequency was a 38% reduction on lamotrigine compared with placebo (P=0.01).
No differences in efficacy based on age, sex, or race, as measured by change in seizure frequency, were detected.
Adjunctive Therapy with Lamotrigine in Pediatric Patients with Partial-Onset Seizures
The effectiveness of lamotrigine as adjunctive therapy in pediatric patients with partial-onset seizures was established in a multicenter, double-blind, placebo-controlled trial in 199 pediatric patients aged 2 to 16 years (n = 98 on lamotrigine, n = 101 on placebo). Following an 8-week baseline phase, patients were randomized to 18 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate use. Target doses were designed to approximate mg/kg doses for patients taking valproate (maximum dose: 250 mg/day) and 15 mg/kg/day for the patients not taking valproate (maximum dose: 750 mg/day). The primary efficacy endpoint was percentage change from baseline in all partial-onset seizures. For the intent-to-treat population, the median reduction of all partial-onset seizures was 36% in patients treated with lamotrigine and 7% on placebo, a difference that was statistically significant (P=0.01).
Adjunctive Therapy with Lamotrigine in Pediatric and Adult Patients with Lennox-Gastaut Syndrome
The effectiveness of lamotrigine as adjunctive therapy in patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on lamotrigine, n = 90 on placebo). Following a 4-week baseline phase, patients were randomized to 16 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to 3 drugs. Patients were dosed on a fixed-dose regimen based on body weight and valproate use. Target doses were designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 200 mg/day) and 15 mg/kg/day for patients not taking valproate (maximum dose: 400 mg/day). The primary efficacy endpoint was percentage change from baseline in major motor seizures (atonic, tonic, major myoclonic, and tonic-clonic seizures). For the intent-to-treat population, the median reduction of major motor seizures was 32% in patients treated with lamotrigine and 9% on placebo, a difference that was statistically significant (P=0.05). Drop attacks were significantly reduced by lamotrigine (34%) compared with placebo (9%), as were tonic-clonic seizures (36% reduction versus 10% increase for lamotrigine and placebo, respectively).
Adjunctive Therapy with Lamotrigine in Pediatric and Adult Patients with Primary Generalized Tonic-Clonic Seizures
The effectiveness of lamotrigine as adjunctive therapy in patients with PGTC seizures was established in a multicenter, double-blind, placebo-controlled trial in 117 pediatric and adult patients aged 2 years and older (n = 58 on lamotrigine, n = 59 on placebo). Patients with at least 3 PGTC seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses ranging from 3 to 12 mg/kg/day for pediatric patients and from 200 to 400 mg/day for adult patients based on concomitant AEDs.
The primary efficacy endpoint was percentage change from baseline in PGTC seizures. For the intent-to-treat population, the median percent reduction in PGTC seizures was 66% in patients treated with lamotrigine and 34% on placebo, a difference that was statistically significant (P = 0.006).

14.2 Bipolar Disorder

Adults
The effectiveness of lamotrigine in the maintenance treatment of bipolar I disorder was established in 2 multicenter, double-blind, placebo-controlled trials in adult patients (18 to 82 years) who met DSM-IV criteria for bipolar I disorder. Trial 1 enrolled patients with a current or recent (within 60 days) depressive episode as defined by DSM-IV and Trial 2 included patients with a current or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both trials included a cohort of patients (30% of 404 subjects in Trial 1 and 28% of 171 patients in Trial 2) with rapid cycling bipolar disorder (4 to 9 episodes per year).
In both trials, patients were titrated to a target dose of 200 mg of lamotrigine as add-on therapy or as monotherapy with gradual withdrawal of any psychotropic medications during an 8- to 16-week open-label period. Overall, 81% of 1,305 patients participating in the open-label period were receiving 1 or more other psychotropic medications, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine), valproate, or lithium, during titration of lamotrigine. Patients with a CGI-severity score of 2 or less maintained for 6 consecutive weeks, including at least the final week on monotherapy with lamotrigine, were randomized to a placebo-controlled, double-blind treatment period for up to 18 months. The primary endpoint was TIME time to intervention for a mood episode or one that was emerging, time to discontinuing for either an adverse event that was judged to be related to bipolar disorder, or for lack of efficacy. The mood episode could be depression, mania, hypomania, or a mixed episode.
In Trial 1, patients received double-blind monotherapy with lamotrigine 50 mg/day (n = 50), lamotrigine 200 mg/day (n = 124), lamotrigine 400 mg/day (n = 47), or placebo (n = 121). Lamotrigine (200- and 400-mg/day treatment groups combined) was superior to placebo in delaying the time to occurrence of a mood episode (Figure 1). Separate analyses of the 200- and 400-mg/day dose groups revealed no added benefit from the higher dose.
In Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was superior to placebo in delaying time to occurrence of a mood episode (Figure 2). The mean dose of lamotrigine was about 211 mg/day.
Although these trials were not designed to separately evaluate time to the occurrence of depression or mania, a combined analysis for the 2 trials revealed a statistically significant benefit for lamotrigine over placebo in delaying the time to occurrence of both depression and mania, although the finding was more robust for depression.

Figure 1: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Mood Episode (Trial 1)

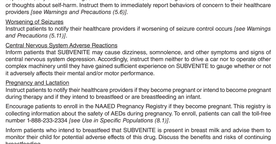
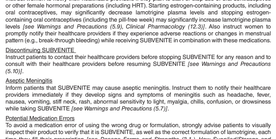


Figure 2: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Mood Episode (Trial 2)



16 HOW SUPPLIED/STORAGE AND HANDLING

14.1 Epilepsy

SUBVENITE (lamotrigine) oral suspension contains 10 mg/mL lamotrigine. It is a pink, cherry-flavored suspension and is supplied in high-density polyethylene (HDPE) bottles with white, polypropylene, child-resistant closures with a foam liner and heat induction layered inner seal:
8 oz (240 mL), NDC 69102-418-01
2 x 8 oz (480mL), NDC 69102-418-02

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Discard the unused portion 90 days after first opening.

PATIENT COUNSELING INFORMATION

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

Rash
Prior to initiation of treatment with SUBVENITE, inform patients that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and instruct them to report any such occurrence to their healthcare providers immediately *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Administration
Instruct patients or caregivers that a calibrated measuring device, such as an oral dosing syringe or oral dosing cup, should be obtained from the pharmacy to accurately measure and deliver the prescribed dose of medication. A household teaspoon or tablespoon is not an adequate measuring device.
Instruct patients to shake well before each use and to discard any unused portion 90 days after first opening the bottle.

Hemophagocytic Lymphohistiocytosis
Prior to initiation of treatment with SUBVENITE, inform patients that excessive immune activation may occur in some patients and that they should report signs or symptoms such as fever, rash, or lymphadenopathy to a physician immediately *[see Warnings and Precautions (5.2)]*.

DRESS/Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ Failure
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. SUBVENITE should be discontinued immediately if a serious hypersensitivity reaction is suspected. Isolated organ failure or isolated