HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRIVIACT® safely and effectively. See full prescribing information for BRIVIACT.

BRIVIACT® (brivaracetam) tablets, for oral use, CV
BRIVIACT® (brivaracetam) oral solution, CV
BRIVIACT® (brivaracetam) injection, for intravenous use, CV
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------

BRIVIACT is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage is 50 mg twice daily. Based on individual patient tolerability and therapeutic response, the dosage may be adjusted down to 25 mg twice daily (50 mg per day) or up to 100 mg twice daily (200 mg per day). (2.1)
- BRIVIACT injection may be used when oral administration is temporarily not feasible.
- *Hepatic Impairment:* For all stages of hepatic impairment, the recommended starting dosage is 25 mg twice daily; maximum dosage is 75 mg twice daily. (2.5, 8.7, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg (3)
- Oral solution: 10 mg/mL (3)
- Injection: 50 mg/5 mL single-dose vial (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to brivaracetam or any of the inactive ingredients in BRIVIACT. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Suicidal Behavior and Ideation*: Monitor patients for suicidal behavior and ideation. (5.1)
- *Neurological Adverse Reactions*: Monitor for somnolence and fatigue, and advise patients not to drive or operate machinery until they have gained sufficient experience on BRIVIACT. (5.2)
- *Psychiatric Adverse Reactions*: Behavioral reactions including psychotic symptoms, irritability, depression, aggressive behavior, and anxiety; monitor patients for symptoms. (5.3)
- *Hypersensitivity: Bronchospasm and Angioedema*: Advise patients to seek immediate medical care. Discontinue and do not restart BRIVIACT if hypersensitivity occurs. (5.4)
- *Withdrawal of Antiepileptic Drugs*: BRIVIACT should be gradually withdrawn. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (at least 5% for BRIVIACT and at least 2% more frequently than placebo) are somnolence/sedation, dizziness, fatigue, and nausea/vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 1-844-599-2273 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- *Rifampin:* Because of decreased BRIVIACT concentrations, increasing BRIVIACT dosage in patients on concomitant rifampin is recommended. (2.6, 7.1)
- *Carbamazepine:* Because of increased exposure to carbamazepine metabolite, if tolerability issues arise, consider reducing carbamazepine dosage in patients on concomitant BRIVIACT. (7.2)
- *Phenytoin:* Because phenytoin concentrations can increase, phenytoin levels should be monitored in patients on concomitant BRIVIACT. (7.3)
- *Levetiracetam:* BRIVIACT had no added therapeutic benefit when co-administered with levetiracetam. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BRIVIACT is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

When initiating treatment, gradual dose escalation is not required. The recommended starting dosage is 50 mg twice daily (100 mg per day). Based on individual patient tolerability and therapeutic response, the dosage may be adjusted down to 25 mg twice daily (50 mg per day) or up to 100 mg twice daily (200 mg per day) *[see Clinical Studies (14)]*.

BRIVIACT injection may be used when oral administration is temporarily not feasible. BRIVIACT injection should be administered at the same dosage and same frequency as BRIVIACT tablets and oral solution.

The clinical study experience with BRIVIACT injection is limited to 4 consecutive days of treatment.

2.2 Administration Instructions for BRIVIACT Tablets and BRIVIACT Oral Solution

BRIVIACT can be initiated with either intravenous or oral administration.

BRIVIACT tablets and oral solution may be taken with or without food.

BRIVIACT Tablets
BRIVIACT tablets should be swallowed whole with liquid. BRIVIACT tablets should not be chewed or crushed.

BRIVIACT Oral Solution
A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

When using BRIVIACT oral solution, no dilution is necessary. BRIVIACT oral solution may also be administered using a nasogastric tube or gastrostomy tube.

Discard any unused BRIVIACT oral solution remaining after 5 months of first opening the bottle.

2.3 Preparation and Administration Instructions for BRIVIACT Injection

BRIVIACT injection is for intravenous use only.

Preparation
BRIVIACT injection can be administered intravenously without further dilution or may be mixed with diluents listed below.

Diluents
0.9% Sodium Chloride injection, USP
Lactated Ringer's injection
5% Dextrose injection, USP

Administration
BRIVIACT injection should be administered intravenously over 2 to 15 minutes.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Product with particulate matter or discoloration should not be used. BRIVIACT injection is for single dose only.

Storage and Stability

The diluted solution should not be stored for more than 4 hours at room temperature and may be stored in polyvinyl chloride (PVC) bags. Discard any unused portion of the BRIVIACT injection vial contents.

2.4 Discontinuation of BRIVIACT

Avoid abrupt withdrawal from BRIVIACT in order to minimize the risk of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.5) and Clinical Studies (14)]*.

2.5 Patients with Hepatic Impairment

For all stages of hepatic impairment, the recommended starting dosage is 25 mg twice daily (50 mg per day) and the recommended maximum dosage is 75 mg twice daily (150 mg per day) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.6 Co-administration with Rifampin

Increase the BRIVIACT dosage in patients on concomitant rifampin by up to 100% (i.e., double the dosage) *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 10 mg: white to off white, round, film-coated, and debossed with "u10" on one side.
- 25 mg: grey, oval, film-coated, and debossed with "u25" on one side.
- 50 mg: yellow, oval, film-coated, and debossed with "u50" on one side.
- 75 mg: purple, oval, film-coated, and debossed with “u75” on one side.
- 100 mg: green-grey, oval, film-coated, and debossed with “u100” on one side.

Oral Solution

- 10 mg/mL: slightly viscous, clear, colorless to yellowish, raspberry-flavored liquid.

Injection

- 50 mg in 5 mL in one single-dose vial. It is a clear, colorless, sterile solution.

4 CONTRAINDICATIONS

Hypersensitivity to brivaracetam or any of the inactive ingredients in BRIVIACT (bronchospasm and angioedema have occurred) *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including BRIVIACT, 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 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: Risk of Suicidal Thoughts or Behaviors 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 in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing BRIVIACT 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, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.2 Neurological Adverse Reactions

BRIVIACT causes somnolence, fatigue, dizziness, and disturbance in coordination. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on BRIVIACT to gauge whether it adversely affects their ability to drive or operate machinery.

Somnolence and Fatigue

BRIVIACT causes dose-dependent increases in somnolence and fatigue-related adverse reactions (fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy) *[see Adverse Reactions (6.1)]*. In the Phase 3 controlled adjunctive epilepsy trials, these events were reported in 25% of patients randomized to receive BRIVIACT at least 50 mg/day (20% at 50 mg/day, 26% at 100 mg/day, and 27% at 200 mg/day) compared to 14% of patients who received placebo. The risk is greatest early in treatment but can occur at any time.

Dizziness and Disturbance in Gait and Coordination

BRIVIACT causes adverse reactions related to dizziness and disturbance in gait and coordination (dizziness, vertigo, balance disorder, ataxia, nystagmus, gait disturbance, and abnormal coordination) *[see Adverse Reactions (6.1)]*. In the Phase 3 controlled adjunctive epilepsy trials, these events were reported in 16% of patients randomized to receive BRIVIACT at least 50 mg/day compared to 10% of patients who received placebo. The risk is greatest early in treatment but can occur at any time.

5.3 Psychiatric Adverse Reactions

BRIVIACT causes psychiatric adverse reactions. In the Phase 3 controlled adjunctive epilepsy trials, psychiatric adverse reactions were reported in approximately 13% of patients who received BRIVIACT (at least 50 mg/day) compared to 8% of patients who received placebo. Psychiatric events included both non-psychotic symptoms (irritability, anxiety, nervousness, aggression, belligerence, anger, agitation, restlessness, depression, depressed mood, tearfulness, apathy, altered mood, mood swings, affect lability, psychomotor hyperactivity, abnormal behavior, and adjustment disorder) and psychotic symptoms (psychotic disorder along with hallucination, paranoia, acute psychosis, and psychotic behavior). A total of 1.7% of adult patients treated with BRIVIACT discontinued treatment because of psychiatric reactions compared to 1.3% of patients who received placebo.

5.4 Hypersensitivity: Bronchospasm and Angioedema

BRIVIACT can cause hypersensitivity reactions. Bronchospasm and angioedema have been reported in patients taking BRIVIACT. If a patient develops hypersensitivity reactions after treatment with BRIVIACT, the drug should be discontinued. BRIVIACT is contraindicated in patients with a prior hypersensitivity reaction to brivaracetam or any of the inactive ingredients *[see Contraindications (4)]*.

5.5 Withdrawal of Antiepileptic Drugs

As with most antiepileptic drugs, BRIVIACT should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus *[see Dosage and Administration (2.4) and Clinical Studies (14)]*. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.1)]*
- Neurological Adverse Reactions *[see Warnings and Precautions (5.2)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.3)]*
- Hypersensitivity: Bronchospasm and Angioedema *[see Warnings and Precautions (5.4)]*
- Withdrawal of Antiepileptic Drugs *[see Warnings and Precautions (5.5)]*

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.

In all controlled and uncontrolled trials performed in adult epilepsy patients, BRIVIACT was administered as adjunctive therapy to 2437 patients. Of these patients, 1929 were treated for at least 6 months, 1500 for at least 12 months, 1056 for at least 24 months, and 758 for at least 36 months. A total of 1558 patients (1099 patients treated with BRIVIACT and 459 patients treated with placebo) constituted the safety population in the pooled analysis of Phase 3 placebo-controlled studies in patients with partial-onset seizures (Studies 1, 2, and 3) *[see Clinical Studies (14)]*. The adverse reactions presented in Table 2 are based on this safety population; the median length of treatment in these studies was 12 weeks. Of the patients in those studies, approximately 51% were male, 74% were Caucasian, and the mean age was 38 years.

In the Phase 3 controlled epilepsy studies, adverse events occurred in 68% of patients treated with BRIVIACT and 62% treated with placebo. The most common adverse reactions occurring at a frequency of at least 5% in patients treated with BRIVIACT doses of at least 50 mg/day and greater than placebo were somnolence and sedation (16%), dizziness (12%), fatigue (9%), and nausea and vomiting symptoms (5%).

The discontinuation rates due to adverse events were 5%, 8%, and 7% for patients randomized to receive BRIVIACT at the recommended doses of 50 mg, 100 mg, and 200 mg/day, respectively, compared to 4% in patients randomized to receive placebo.

Table 2 lists adverse reactions for BRIVIACT that occurred at least 2% more frequently for BRIVIACT doses of at least 50 mg/day than placebo.

Table 2: Adverse Reactions in Pooled Placebo-Controlled Adjunctive Therapy Studies in Patients with Partial-Onset Seizures (BRIVIACT 50 mg/day, 100 mg/day, and 200 mg/day)

Adverse Reactions	BRIVIACT (N=803) %	Placebo (N=459) %
Gastrointestinal disorders		
Nausea/vomiting symptoms	5	3
Constipation	2	0
Nervous system disorders		
Somnolence and sedation	16	8
Dizziness	12	7
Fatigue	9	4
Cerebellar coordination and balance disturbances*	3	1

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