New Drug Evaluation: brivaracetam [tablet and solution, oral; solution, intravenous]

Date of Review: July 2016
Generic Name: brivaracetam
PDL Class: Antiepileptics

End Date of Literature Search: March 2016
Brand Name (Manufacturer): Briviact® (UCB Pharmaceuticals)
AMCP Dossier Received:

Research Questions:
• What is the evidence for the efficacy of brivaracetam in treating adults with uncontrolled focal seizures?
• How well is brivaracetam tolerated in patients with uncontrolled epilepsy?
• Based on the evidence available does brivaracetam have a role in therapy for patients with epilepsy?

Conclusions:
• Three short term trials lasting from 16 to 20 weeks evaluated the efficacy of brivaracetam compared to placebo. \(^1,^2,^3\) All of the trials were conducted in adults with uncontrolled focal seizures maintained on 1 to 3 antiepileptic medications. BRV doses between 50 and 100mg significantly reduced seizure frequency in the studied patient population. The seizure events were self-reported by patients, which may have introduced some bias into the primary outcomes the researchers were evaluating of reduction of seizure frequency.
• Tolerability of brivaracetam was similar to placebo. Primary adverse effects included fatigue, somnolence and dizziness. Evaluation of brivaracetam’s long term safety profile is needed.
• More evidence is needed to evaluate the efficacy of brivaracetam as a first line agent in focal seizures. Brivaracetam may be an effective adjunct in patients with uncontrolled focal seizures already maintained on 1-3 antiepileptic therapies.

Recommendations:
• Designate brivaracetam as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMDPD).

Background: Epilepsy affects about 1% of the United States adult population.\(^4\) The main treatment of epilepsy is antiepileptic drug (AED) therapy. Over twenty AED’s are approved for treatment of this syndrome.\(^5\) Drug therapy is generally initiated after two or more unprovoked seizures. Approximately one third of patients experience seizures despite pharmacotherapy.\(^6\) Selection of medication therapy is based on type of seizure, adverse effects associated with the medication, and patient specific parameters. Many AED’s are associated with increased risk for impaired psychomotor function resulting in increased fall risk and the possibility of a fracture. All AED’s carry an FDA “black box” warning regarding the risk of suicidal thinking associated with their use. Some AED’s (ex: valproate) may cause fetal malformations or neurodevelopment impairment and should be avoided during pregnancy. Drug interactions can occur with certain AED’s due to hepatic enzyme induction or inhibition depending on which medications are concurrently administered. Most of the newer AED’s have been

Author: Deanna Moretz, PharmD
Date: May 2016
developed in an effort to improve safety and tolerability. The U.K.’s National Institute for Health Care and Excellence (NICE) epilepsy guidelines provide an outline with detailed prescribing considerations for the different AED’s.7

Seizures are broadly classified as either generalized or focal. According to the International League Against Epilepsy (ILAE) definition, generalized seizures arise within bilaterally distributed networks while focal seizure originate within a network limited to one hemisphere of the brain.8 Brivaracetam (BRV) has primarily been evaluated in adult focal seizures. According to the 2012 NICE epilepsy treatment guidelines, first line agents for treatment of focal seizures include carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, and valproate. Second line agents include clobazam, gabapentin, and topiramate. Other agents that may be effective include lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide. Monotherapy is preferred to reduce adverse effects and enhance quality of life.9 Very few studies have evaluated drug combinations in randomized controlled trials. A 2011 meta-analysis focused on the clinical comparability of AED’s used as adjunctive therapy in patients with refractory focal epilepsy. Sixty-two placebo controlled and eight head to head randomized controlled trials were included in the review. The primary objectives were to evaluate seizure reduction and tolerability rates. The authors found very small differences between AED therapies and concluded that no single AED showed more effectiveness over other agents as add on therapy. Withdrawal rates were higher with oxcarbazepine (OR 1.60; 1.12-2.29) and topiramate (OR 1.68; 1.07-2.63) and lower with gabapentin (OR 0.65; 0.42-1.00) and levetiracetam (OR 0.62; 0.43-0.89).10 Given the paucity of evidence, general consensus is to choose add on medications with a different mechanism of action and a different adverse event profile than the first AED on which the patient was started.

See Appendix 1 for Highlights of Prescribing Information from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Three phase 3 trials assessed the short-term efficacy and safety of brivaracetam. Brivaracetam (BRV), an analog of levetiracetam, is a selective high affinity synaptic vesicle protein 2A ligand. In study N01254 adjunctive BRV was administered in doses ranging from 20 to 150 mg per day in adults with uncontrolled epilepsy during an 8 week dose finding period. An 8 week stable dose maintenance period followed the initial phase. The study population included patients with focal epilepsy (90%) and generalized epilepsy (10%). In the cohort of patients with focal seizures the percent reduction in seizure frequency from baseline compared to placebo was 7.3% and did not reach statistical significance (p=0.125). The median percent reduction in seizure frequency was 26.9% for BRV versus 16.7% for placebo (p=0.070). The greater than 50% responder rate for BRV (30.3%) was statistically significant (p=0.006) compared to placebo (16.7%). Because BRV showed efficacy across some outcome measures the authors concluded that further efficacy studies for BRV were warranted.

Study N01252 was a double-blind, randomized, placebo controlled trial. Patients were randomized to 3 doses of BRV (20, 50, and 100mg per day) or placebo in adults with uncontrolled focal seizures despite treatment with one or two concomitant antiepileptic drugs over a 12 week treatment period. Only the 100 mg dose showed statistical significance (p= 0.037) over placebo in reducing seizure frequency per week by 11.7%. Patients treated with BRV 20mg per day noted a 6.8% (p = 0.239) percent reduction in seizure frequency and the 50mg per day dose showed a 6.5% decrease in seizures (p=0.261). Study N01253 was a double blind randomized controlled trial in adults with focal epilepsy. In the first 8 weeks patients were randomized to receive placebo or BRV 5, 20 or 50mg per day without dose titration. The primary endpoint of seizure reduction was evaluated during the 12 week treatment period. Significant percent reduction in seizure frequency over placebo was only noted with BRV 50mg per day (12.8% reduction p=0.025). The other two dosing regimens did not achieve statistical significance in reducing seizure frequency (BRV 5mg = -0.9%, p = 0.885 and BRV 20mg = 4.1% p = 0.492). In conclusion, based on the results of these trials, brivaracetam may be an effective adjunct in treating adult patients with uncontrolled focal seizures that have not been effectively managed with other antiepileptic medications.
Clinical Safety:
The majority of adverse events observed in short-term phase 3 trials were mild to moderate in severity. Headache, somnolence, dizziness, and fatigue were the most commonly reported adverse events. Adverse events that resulted in premature discontinuation of the studies were relatively similar across all BRV doses and placebo-treated groups in N01252 but early discontinuations were much higher in the BRV-treated groups in N01253. The most commonly reported adverse events that led to premature study discontinuation were psychiatric disorders (i.e., aggression, anxiety, irritability, depression and insomnia).

In N01252, serious adverse events (a life-threatening event, or an event resulting in death, permanent or significant disability, a congenital birth defect, or hospitalization) occurred more often in placebo-treated subjects (6%) than BRV-treated patients (2.3%). There were no clinically significant changes from baseline in laboratory parameters (blood chemistry or urinalysis), body weight, vital signs or ECG measurements. In N01253, serious adverse events occurred more often in BRV-treated patients (2.3%) than placebo-treated subjects (0%). In addition, 2 subjects died from the BRV 50 mg/day group. One subject died from cardiorespiratory arrest following a seizure on the first day of the dose taper period immediately following the final 12-week follow-up. The second subject died from a large subarachnoid hemorrhage 2 weeks after discontinuing the study drug. There were no clinically significant changes from baseline in laboratory parameters (blood chemistry or urinalysis), body weight, vital signs or ECG measurements. In N01254, serious adverse events occurred in 5.3% of the BRV-treated subjects and 7.4% of the placebo-treated subjects. The most frequently reported SAEs were convulsions (n=10: BRV 2.8%, PBO 0.8%) and status epilepticus (n=3, all occurred in one BRV-treated subject). One death occurred in a BRV-treated subject who drowned after experiencing a convulsion while swimming. There were no clinically significant changes from baseline in laboratory parameters (blood chemistry or urinalysis), body weight, or vital signs. However, there were 3 BRV-treated subjects that experienced ECG abnormalities of sinus bradycardia.

Look-alike / Sound-alike Error Risk Potential: None identified

Pharmacology and Pharmacokinetic Properties:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>High affinity ligand for SV2A (similar to LEV). The precise role of the protein in neurotransmission is unclear but SV2A-binding affinity is strongly correlated with anticonvulsant potency in animal models and low levels of SV2A are correlated with seizures in animal models.</td>
</tr>
<tr>
<td>Absorption</td>
<td>Rapidly absorbed through GI tract with ~100% bioavailability</td>
</tr>
<tr>
<td>Distribution and</td>
<td>Weakly bound to plasma proteins (&lt;20%)</td>
</tr>
<tr>
<td>Protein Binding</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Extensively transformed into 3 major metabolites</td>
</tr>
<tr>
<td>Half-Life</td>
<td>7-8 hours</td>
</tr>
<tr>
<td>Elimination</td>
<td>&gt;95%urine, &lt;1%feces</td>
</tr>
</tbody>
</table>

Abbreviations: AED = antiepileptic drugs; GI = gastrointestinal; LEV = levetiracetam; SV2A = synaptic vesicle protein 2A.
Comparative Clinical Efficacy:
Clinically Relevant Endpoints:
1) Seizure reduction (all types)
2) Hospitalizations
3) Adverse events leading to withdrawal from study

Primary Study Endpoint:
1) Median percent reduction in focal seizures from baseline versus placebo
## Comparative Evidence Table

<table>
<thead>
<tr>
<th>Ref./Study Design</th>
<th>Drug Regimens/Duration</th>
<th>Patient Population</th>
<th>N</th>
<th>Efficacy Endpoints</th>
<th>ARR/NNT</th>
<th>Safety Outcomes</th>
<th>ARR/NNH</th>
<th>Risk of Bias/Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ryvlin, et al.(^1)</td>
<td>1. BRV 10 mg BID</td>
<td>Demographics: -Mean age: 37.2 y -Male: 57.0% -White: 76.6% -Mean duration of epilepsy: 21.8 y -Focal seizures/week: 1.95 -≥2 concomitant AEDs: 78.9%</td>
<td>mITT: 1. 99 2. 99 3. 100 4. 100</td>
<td>Primary Endpoint: Median % reduction vs. PBO from baseline in self-reported focal seizures/week: 1. 6.8% (95% CI, -4.8 to 17.1%; p=0.239) 2. 6.5% (95% CI, -5.2 to 16.9; p=0.261) 3. 11.7% (95% CI, 0.7 to 21.4%; p=0.037)</td>
<td>D/C due to AE: 1. 4.0% 2. 5.1% 3. 5.0% 4. 4.0% p-values NR</td>
<td>Drug-related AE: 1. 23.2% 2. 37.4% 3. 42.0% 4. 31.0% p-values NR</td>
<td>NA for all</td>
<td>Risk of Bias (low/high/unclear): Selection Bias: unclear. Central randomization by IVRS stratified by geographic region and concomitant LEV use (of which was limited to 20% per group). Performance Bias: unclear. Method of blinding not stated; unclear if double-dummy design. Vagus nerve stimulation, BZD use b/w groups unknown. Assigned dose could be reduced once, which placed patients into a different study arm than originally allocated. Attrition Bias: Low. mITT performed but all but 1 patient randomized were analyzed. At 12 weeks, attrition rates were low, similar. Reporting Bias: Low. Outcomes reported as prespecified.</td>
</tr>
<tr>
<td></td>
<td>2. BRV 25 mg BID</td>
<td>Key Inclusion Criteria: -Age 16-70 y -Focal epilepsy -Uncontrolled focal seizures (≥2 focal seizures per month in 3 months) ≥8 focal seizures during 8-week baseline period -1-2 concomitant AED (inc LEV or BZD) before and during study</td>
<td></td>
<td>Secondary Endpoints: Median % reduction in self-reported focal seizures/week from baseline: 1. 30.0% (p=0.019 vs. PBO) 2. 26.8% (p=0.092 vs. PBO) 3. 32.5% (p=0.004 vs. PBO) 4. 17.0%</td>
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<td></td>
<td>3. BRV 50 mg BID</td>
<td>Key Exclusion Criteria: -Nonmotor simple focal seizures -h/o seizures only occurring in clusters -h/o status epilepticus</td>
<td></td>
<td>≥50% responder rate (≥50% reduction from baseline in self-reported focal seizures/week): 1. 27.3% (p=0 vs. PBO) 2. 27.3% (p=0 vs. PBO) 3. 36.0% (p=0 vs. PBO) 4. 20.0%</td>
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<tr>
<td>1:1:1:1</td>
<td>4. PBO BID</td>
<td>12 weeks</td>
<td>Attrition: 1. 6% 2. 11% 3. 6% 4. 8%</td>
<td>Seizure-free (no reported seizures of any kind): 1. 2% 2. 0% 3. 4% 4. 0%</td>
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</table>

### Key Inclusion Criteria:
- Age 16-70 y
- Focal epilepsy
- Uncontrolled focal seizures (≥2 focal seizures per month in 3 months)
- ≥8 focal seizures during 8-week baseline period
- 1-2 concomitant AED (inc LEV or BZD) before and during study

### Key Exclusion Criteria:
- Nonmotor simple focal seizures
- h/o seizures only occurring in clusters
- h/o status epilepticus

### Patient Population:
- Mean age: 37.2 y
- Male: 57.0%
- White: 76.6%
- Mean duration of epilepsy: 21.8 y
- Focal seizures/week: 1.95
- ≥2 concomitant AEDs: 78.9%

### Study Design:
- MC, DB, PC, PG, RCT
- Phase 3
- N01252

### Drug Regimens/Duration:
1. BRV 10 mg BID
2. BRV 25 mg BID
3. BRV 50 mg BID
4. PBO BID

### Duration:
12 weeks

### Efficacy Endpoints:
- Median % reduction vs. PBO from baseline in self-reported focal seizures/week:
  - 1. 6.8% (95% CI, -4.8 to 17.1%; p=0.239)
  - 2. 6.5% (95% CI, -5.2 to 16.9; p=0.261)
  - 3. 11.7% (95% CI, 0.7 to 21.4%; p=0.037)

### Safety Outcomes:
- D/C due to AE:
  - 1. 4.0%
  - 2. 5.1%
  - 3. 5.0%
  - 4. 4.0%
  - p-values NR

### Comparator:
- Placebo control appropriate; concomitant AEDs were relatively equal across all groups.

### Setting:
- 88 sites in Europe and India. Subjects evaluated at baseline, week 2, 4, 8 and 12. Final safety visit at week 16 after dose tapered off.

### Author:
Deanna Moretz, PharmD

### Date:
May 2016
<table>
<thead>
<tr>
<th></th>
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<th>Demographics:</th>
<th>mITT</th>
<th>Primary Endpoint:</th>
<th>D/C due to AE:</th>
<th>NA for all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BRV 2.5 mg BID</td>
<td>-Mean age: 38.2 y</td>
<td>1.96</td>
<td>Median % reduction vs. PBO from baseline in self-reported focal seizures/week:</td>
<td>1. 8.2%</td>
<td>NA</td>
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<tr>
<td>2</td>
<td>BRV 10 mg BID</td>
<td>-Male: 49.2%</td>
<td>2.99</td>
<td>1. -0.9% (95% CI NR; p=0.885)</td>
<td>2. 4.0%</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>BRV 25 mg BID</td>
<td>-White: 72.2%</td>
<td>3.101</td>
<td>2. 4.1% (95% CI NR; p=0.492)</td>
<td>3. 5.5%</td>
<td>NS</td>
</tr>
<tr>
<td>4</td>
<td>PBO BID</td>
<td>-Mean duration of epilepsy: 24.0 y</td>
<td>4.96</td>
<td>3. 12.8% (95% CI NR; p=0.025)</td>
<td>4. 2.0%</td>
<td>NA</td>
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</table>

**Attrition:**

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<tr>
<td>1</td>
<td>1.5%</td>
<td>2</td>
<td>2.7%</td>
<td>3</td>
<td>3.8%</td>
<td>4</td>
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</tbody>
</table>

**Key Inclusion Criteria:** See N01252

**Key Exclusion Criteria:** See N01252

**Demographics:**

- Mean age: 38.2 y
- Male: 49.2%
- White: 72.2%
- Mean duration of epilepsy: 24.0 y
- Focal seizures/week: 2.5
- ≥2 concomitant AEDs: 85.6%

**Primary Endpoint:** Median % reduction vs. PBO from baseline in self-reported focal seizures/week:

1. -0.9% (95% CI NR; p=0.885)
2. 4.1% (95% CI NR; p=0.492)
3. 12.8% (95% CI NR; p=0.025)

**Secondary Endpoints:** Median % reduction in self-reported focal seizures/week from baseline:

1. 20.0% (p=0.991 vs. PBO)
2. 22.5% (p=0.38 vs. PBO)
3. 30.5% (p=0.003 vs. PBO)
4. 17.8%

**≥50% responder rate (≥50% reduction from baseline in self-reported focal seizures/week):**

1. 21.9% (p=0.353 vs. PBO)
2. 23.2% (p=0.239 vs. PBO)
3. 32.7% (p=0.008 vs. PBO)
4. 16.7%

**Seizure-free (no reported seizures of any kind):**

1. 1.1%
2. 1.0%
3. 4.0%
4. 0%

**Risk of Bias (low/high/unclear):**

- Selection Bias: unclear. Central randomization by IVRS stratified by geographic region and concomitant LEV use (of which was limited to 20% per group).
- Performance Bias: unclear. Described as “matching placebo” with patients and investigators blinded to treatment. Vagus nerve stimulation, BZD use b/w groups unknown. Assigned dose could be reduced once, which placed patients into a different study arm than originally allocated.
- Detection Bias: unclear. Unknown if data assessors blinded or if seizures were self-reported. Statistical tests utilized appropriate. Study powered; assumptions stated but not referenced. Imputation of data unknown.
- Attrition Bias: High. mITT performed (≥1 dose received), which excluded 8 patients allocated to groups, including 4 patients due to randomization errors.
- Reporting Bias: Low. Outcomes reported as prespecified.

**Applicability:**

- Patient: Young or middle-aged adult males and females, diverse racial groups w/ h/o focal seizures since childhood; experience about 2.5 focal seizures per week on multiple AEDs (carbamazepine, > lamotrigine, > LEV, > phenytoin, > valproic acid, > oxcarbazepine).
- Intervention: Used as an adjunctive agent (3rd or 4th line); doses studied lower than FDA-approved doses. Formulation unknown. Doses tapered off at end of study or were enrolled into open-label long-term study.
- Comparator: Placebo appropriate; concomitant AEDs were relatively equal across all groups.
- Outcomes: Absolute reduction in seizure frequency/week would be more clear. Safety outcomes limited to treatment period only.
- Setting: 85 sites in North America, Mexico, Brazil and Australia. Follow-up intervals not specified.
3. Kwan, et al.\(^2\)

**MC, DB, PC, PG, RCT**

**Phase 3 N01254**

1. BRV 10 mg BID, titrated at 2-week intervals to 25 mg, 50 mg or 75 mg BID as tolerated during 8 week dose-finding period
2. PBO BID
3:1
8-week dosing-finding period, followed by 8-week maintenance period

<table>
<thead>
<tr>
<th>Demographics:</th>
<th>mITT: 1. n=359 2. n=121</th>
<th>Primary Endpoint: Median % reduction vs. PBO from baseline in self-reported focal seizures/week:</th>
<th>Na for all</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRV, PBO: 35.6 y, 36.5 y&lt;br&gt;Male BRV, PBO: 50.4%, 57.0%&lt;br&gt;White BRV, PBO: 58.2%, 57.0%&lt;br&gt;Mean duration of epilepsy BRV, PBO: 21.2 y, 22.0 y&lt;br&gt;Focal seizures: 89.8%&lt;br&gt;≥2 concomitant AEDs: 82.7%&lt;br&gt;Median focal seizures/week BRV, PBO: 1.42, 1.47</td>
<td>1. 7.3% (p=0.125)</td>
<td>1. D/C due to AE: 6.1%&lt;br&gt;2. 5.0%&lt;br&gt;p-values NR&lt;br&gt;SAE: 1. 5.3%&lt;br&gt;2. 7.4%&lt;br&gt;p-values NR&lt;br&gt;Headache: 1. 14.2%&lt;br&gt;2. 19.8%&lt;br&gt;p-values NR&lt;br&gt;Somnolence: 1. 11.1%&lt;br&gt;2. 4.1%&lt;br&gt;p-values NR&lt;br&gt;Dizziness: 1. 8.6%&lt;br&gt;2. 5.8%&lt;br&gt;p-values NR&lt;br&gt;Fatigue: 1. 7.8%&lt;br&gt;2. 4.1%&lt;br&gt;p-values NR&lt;br&gt;Psychiatric AEs: 1. 12.3%&lt;br&gt;2. 11.6%&lt;br&gt;p-values NR</td>
<td>13.6%/8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Attrition: 1. 10% 2. 8%</th>
<th>Secondary Endpoints (reported only in focal seizure mITT population only): Median % reduction in self-reported focal seizures/week from baseline:</th>
<th>NA for all</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% responder rate (≥50% reduction from baseline in self-reported focal seizures/week):</td>
<td>1. 30.3% (p=0.006 vs. PBO) 2. 16.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Seizure-free (no reported seizures of any kind):</td>
<td>1. 1.5% (p=0.337 vs. PBO) 2. 0%</td>
<td>NS</td>
</tr>
<tr>
<td>Exploratory endpoints in the generalized seizure mITT population are not reported.</td>
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</tbody>
</table>

**Risk of Bias (low/high/unclear):**

**Selection Bias:** unclear. Randomization process unclear; performed by permuted blocks; stratified by epilepsy type (focal or generalized), LEV use and geographic region. h/o generalized seizure and LEV use was limited to 20% in each arm.

**Performance Bias:** unclear. Described as “matching placebo” with patients and investigators blinded to treatment. Vagus nerve stimulation, BZD use b/w groups unknown.

**Detection Bias:** unclear. Unknown if data assessors blinded. Seizures were self-reported on daily record cards; missed recordings could not be accounted for. Statistical tests utilized appropriate. Study powered; based on secondary efficacy endpoint; assumptions stated and referenced. Imputation of data unknown.

**Attrition Bias:** High. mITT performed (≥1 dose received) and 63/543 subjects excluded from analysis.

**Reporting Bias:** Low. Multiple subgroup analyses were prespecified.

**Applicability:**

**Patient:** Young or middle-aged adult white or Asian males and females w/ h/o focal seizures since childhood; experience about 1.5 focal seizures per week on multiple AEDs (carbamazepine, >valproic acid, >lamotrigine, >topiramate, >LEV).

**Intervention:** 25.1% received 100 mg/d; 51.8% received 150 mg/d. Formulation unknown. Doses tapered off over 1-3 weeks at end of study or were enrolled into open-label long-term study.

**Comparator:** Placebo appropriate; concomitant AEDs were relatively equal across all groups.

**Outcomes:** Primary objective of study was to assess safety outcomes, but study was powered to assess % reduction in focal seizures versus placebo.

**Setting:** 74 sites in Asia and Europe.
Abbreviations [alphabetical order]: AE = adverse events; AED = antiepileptic drug; ARR = absolute risk reduction; BID = twice daily; BRV = brivaracetam; BZD = benzodiazepine; CI = confidence interval; DB = double blinded; h/o = history of; ITT = intention to treat; IVRS = interactive voice response system; LEV = levetiracetam; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PC = placebo-controlled; PBO = placebo; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SAE = serious adverse events (a life-threatening event, or an event resulting in death, permanent or significant disability, a congenital birth defect, or hospitalization)
References:


Appendix 1: Highlights of Prescribing Information

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
BRIVIACT® (brivaracetam) oral solution
BRIVIACT® (brivaracetam) injection, for intravenous use
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)

-------------------DOSE 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)

-------------------DOSE 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.

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