Drug Use Research & Management Program
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New Drug Evaluation: brivaracetam [tablet and solution, oral; solution, intravenous]

Date of Review: July 2016
Generic Name: brivaracetam
PDL Class: Antiepileptic Drugs

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

Research Questions:

- What is the evidence for the efficacy of brivaracetam (BRV) in treating adults with uncontrolled focal seizures and how does it compare to other antiepileptic drug (AED) therapy?
- How well is BRV tolerated in patients with uncontrolled epilepsy and does it compare to other AED therapy?
- Based on the evidence available does BRV have a role in therapy for patients with epilepsy?

Conclusions:

- Three short-term, industry-sponsored, multi-national Phase 3 trials of unclear risk of bias and uncertain applicability lasting from 8-12 weeks evaluated the efficacy of oral brivaracetam compared to placebo. [1-3] Intravenous formulations were not studied in clinical trials. All 3 trials were conducted in adults with uncontrolled focal seizures maintained on 1 to 3 antiepileptic medications. Daily BRV doses between 50 and 150 mg statistically significantly reduced seizure frequency in the studied patient population. These trials provide low quality evidence that adjunctive use of BRV may reduce seizures by 7-12% versus placebo. Seizure events were self-reported by patients, which may have introduced some bias into reporting the primary outcome of reduced seizure frequency.
- There is insufficient comparative evidence to evaluate efficacy or harms data of BRV with other AED therapies.
- Tolerability of BRV was similar to placebo. Primary adverse effects included fatigue, somnolence and dizziness.
- There is insufficient evidence to evaluate the efficacy and long-term safety of BRV and what role it might play as an adjunct for management of focal seizures.

Recommendations:

- Maintain BRV as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).

Background: Epilepsy affects about 1% of the United States adult population.[4] The main treatment of epilepsy is antiepileptic drug (AED) therapy. Over 20 AEDs are approved for treatment of seizures.[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 AEDs are associated with increased risk for impaired psychomotor function resulting in increased fall risk and the possibility

of a fracture. All AEDs carry an FDA "black box" warning regarding the risk of suicidal thinking associated with their use. Some AEDs (e.g., valproate) may cause fetal malformations or neurodevelopment impairment and should be avoided during pregnancy. Drug interactions can occur with certain AEDs due to hepatic enzyme induction or inhibition depending on which medications are concurrently administered. Most of the newer AEDs have been 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 AEDs.[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. A 2011 meta-analysis focused on the clinical comparability of AEDs used as adjunctive therapy in patients with refractory focal epilepsy. Sixty-two placebo-controlled and 8 head-to-head RCTs 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; 95% confidence interval [CI], 1.12-2.29) and topiramate (OR 1.68; 95% CI, 1.07-2.63) and lower with gabapentin (OR 0.65; 95% CI, 0.42-1.00) and levetiracetam (OR 0.62; 95% CI, 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 multi-national phase 3 RCTs with unclear risk of bias and uncertain applicability assessed the short-term efficacy and safety of BRV (see Evidence Table for details below). Brivaracetam, 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%). The primary objective in this study was to confirm safety and tolerability of BRV. The proportion of patients reporting at least 1 concomitant AED was similar in the BRV (66%) and placebo (65.3%) arms. The most commonly reported side effects included headache, somnolence and dizziness. The discontinuation rate due to AE's was similar in both groups (BRV 6.1%, placebo 5%). In the cohort of patients with focal seizures, the absolute percent reduction in seizure frequency from baseline compared to placebo was 7.3% and did not reach statistical significance (p=0.125). Confidence intervals were not reported by the authors. The median percent reduction in seizure frequency was 26.9% for BRV versus 16.7% for placebo (p=0.070). The 50% or greater response rate (defined as ≥50% relative reduction in self-reported seizures from baseline) for BRV (30.3%) was statistically significant (p=0.006) compared to placebo (16.7%). The authors concluded BRV was well tolerated in adults with uncontrolled epilepsy, but further evaluation of efficacy in reducing focal seizures was needed.

Study N01252 was a double-blind, placebo-controlled RCT. Patients were randomized to 3 doses of BRV (20, 50, and 100 mg per day) or placebo in adults with uncontrolled focal seizures despite treatment with 1-2 concomitant AEDs over a 12-week treatment period. The primary outcome evaluated in this study was

the focal seizure frequency per week over the treatment period. Patients reported the occurrence of seizures on daily record cards, which were reviewed with the investigators at each study visit. The study did not meet statistical significance for the primary efficacy endpoint and the authors did not provide a statistical analysis of the primary outcome in their report. The analysis of percent reduction over placebo in focal seizure frequency per week were not significant for the 20 mg per day (6.8%; 95% CI, -4.8-17.1%) or the 50 mg per day (6.5%; 95% CI -5.2-16.9%) arms. However, the 100 mg per day arm did show statistical significance (11.7%; 95% CI 0.7-21.4%).

Study N01253 was also 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 50 mg per day without dose titration. The primary endpoint of median seizure reduction was evaluated during the 12-week treatment period. Significant median percent reduction in seizure frequency over placebo was only noted with BRV 50 mg per day (12.8%; p=0.025). The other 2 dosing regimens did not achieve statistical significance in reducing seizure frequency (BRV 5 mg = -0.9%, p = 0.885 and BRV 20 mg = 4.1%, p = 0.492). Confidence intervals were not reported by the authors. In conclusion, based on the results of these low quality 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.

An additional 12 week, randomized, double blind, placebo controlled trial evaluated 760 adults with uncontrolled focal seizures despite treatment with 1-2 antiepileptic drugs. Patients were randomized to receive placebo, BRV 100mg/day or BRV 200mg/day. The co-primary outcomes were percent reduction over placebo in seizure frequency and ≥ 50% responder rate based on percent reduction in seizure frequency. Percent reduction over placebo in 28-day adjusted seizure frequency (95% confidence interval [CI]) was 22.8% for BRV 100 mg/day (13.3-31.2%; $p < 0.001$) and 23.2% for BRV 200 mg/day (13.8-31.6%; $p < 0.001$). The ≥ 50% responder rate (odds ratio vs. PBO; 95% CI) was 21.6% for PBO, 38.9% for BRV 100 mg/day (2.39; 1.6-3.6; $p < 0.001$), and 37.8% for BRV 200 mg/day (2.19; 1.5-3.3; $p < 0.001$).[11] In conclusion, based on the results of these low quality 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 per 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:

Parameter	
Mechanism of Action	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.
Absorption	Rapidly absorbed through GI tract with ~100% bioavailability
Distribution and Protein Binding	Weakly bound to plasma proteins (<20%)
Metabolism	Extensively transformed into 3 major metabolites
Half-Life	7-8 hours
Elimination	>95%urine, <1%feces

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

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Ryvlin, et al.[1] MC, DB, PC, PG, RCT Phase 3 N01252	1. BRV 10 mg BID 2. BRV 25 mg BID 3. BRV 50 mg BID 4. PBO BID 1:1:1:1 12 weeks	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% Key Inclusion Criteria: -Age 16-70 y -Focal epilepsy -Uncontrolled focal seizures (h/o ≥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	mITT: 1. 99 2. 99 3. 100 4. 100 Attrition: 1. 6% 2. 11% 3. 6% 4. 8%	Primary Endpoint: Median focal seizure frequency/week over 8 weeks (Q1-Q3 -25-75th percentile) 1. 1.34 (0.70-3.12) 2. 1.49 (0.69-2.78) 3. 1.26 (0.52-2.93) 4. 1.75 (0.76-5.12) Secondary 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) 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% ≥50% responder rate (≥50% reduction from baseline in self-reported focal seizures/week): 1. 27.3% (p=0.339. vs. PBO) 2. 27.3% (p=0.3720. vs. PBO) 3. 36.0% (p=0.0230. vs. PBO) 4. 20.0% Seizure-free: 1. 2% 2. 0% 3. 4% 4. 0%	NA NA NA NS NS NA NA NS NA NS NS 16%/7 NR NR NR	D/C due to AE: 1. 4.0% 2. 5.1% 3. 5.0% 4. 4.0% p-values NR Drug-related AE: 1. 23.2% 2. 37.4% 3. 42.0% 4. 31.0% p-values NR SAE: 1. 1.0% 2. 4.0% 3. 2.0% 4. 6.0% p-values NR Headache: 1. 14.1% 2. 18.2% 3. 9.0% 4. 9.0% p-values NR Somnolence: 1. 8.1% 2. 6.1% 3. 8.0% 4. 9.0% p-values NR Fatigue: 1. 3.0% 2. 4.0% 3. 8.0% 4. 2.0% p-values NR	NA for all	**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. Detection Bias: High. Unknown if data assessors blinded. Seizures were self-reported. Statistical tests utilized appropriate. Study powered; assumptions stated but not referenced. Imputation of data unknown. Attrition Bias: Low. mITT performed but all but 1 patient randomized were analyzed. At 12 weeks, attrition rates were low, similar. Reporting Bias: High. Statistical analysis of primary outcome not completed. Funded by UCB Pharma. **Applicability**: Patient: Young or middle-aged adult males and females, mostly white race w/ h/o focal seizures since childhood; experience about 2 focal seizures per week on multiple AEDs (carbamazepine >valproic acid >lamotrigine >oxcarbazepine >LEV). Intervention: Used as an adjunctive agent (3rd or 4th line). Formulation unknown. Doses tapered off at end of study or were enrolled into long-term, open-label study. Comparator: active control more appropriate; concomitant AEDs were relatively equal across all groups. Outcomes: Absolute reduction in seizure frequency/week would be more clear. Safety outcomes observed only until week 16. Setting: 88 sites in Europe and India. No U.S> sites. Subjects evaluated at baseline, week 2, 4, 8 and 12.

Author: Moretz

Date: July 2016

2. Biton, et al.[2] MC, DB, PC, PG, RCT Phase 3 N01253	1. BRV 2.5 mg BID 2. BRV 10 mg BID 3. BRV 25 mg BID 4. PBO BID 1:1:1:1 12 weeks	<u>Demographics</u>: -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% <u>Key Inclusion Criteria</u>: See N01252 <u>Key Exclusion Criteria</u>: - See N01252	<u>mITT</u>: 1. 96 2. 99 3. 101 4. 96 <u>Attrition</u>: 1. 15% 2. 7% 3. 8% 4. 5%	<u>Primary Endpoint</u>: 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) <u>Secondary Endpoints</u>: Median % reduction in self-reported focal seizures/week from baseline: 1. 20.0% (p=0.991 vs. PBO) 2. 22.5% (p=0.386 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%	 NS NS NA NS NS NA NS NS 16%/7 NR NR NR	<u>D/C due to AE</u>: 1. 8.2% 2. 4.0% 3. 5.9% 4. 2.0% p-values NR <u>Drug-related AE</u>: 1. 44.3% 2. 46.0% 3. 55.4% 4. 35.7% p-values NR <u>SAE</u>: 1. 1.0% 2. 2.0% 3. 3.0% 4. 0% p-values NR <u>Headache</u>: 1. 11.3% 2. 6.0% 3. 12.9% 4. 14.3% p-values NR <u>Somnolence</u>: 1. 14.4% 2. 14.0% 3. 16.8% 4. 7.1% p-values NR <u>Dizziness</u>: 1. 12.4% 2. 14.0% 3. 15.8% 4. 9.2% p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: unclear. Central randomization by IVRS stratified by geographic region and concomitant LEV use (of which was limited to 20% per group). <u>Performance Bias</u>: 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. <u>Detection Bias</u>: 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. <u>Attrition Bias</u>: High. mITT performed (≥1 dose received), which excluded 8 patients allocated to groups, including 4 patients due to randomization errors. <u>Reporting Bias</u>: Low. Outcomes reported as prespecified. Funded by UCB Pharma. **Applicability**: <u>Patient</u>: 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). <u>Intervention</u>: 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. <u>Comparator</u>: active control more appropriate; concomitant AEDs were relatively equal across all groups. <u>Outcomes</u>: Absolute reduction in seizure frequency/week would be more clear. Safety outcomes limited to treatment period only. <u>Setting</u>: 85 sites in North America, Mexico, Brazil and Australia. Follow-up intervals not specified.

3. Kwan, et al.[3] 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	Demographics: -Mean age BRV, PBO: 35.6 y, 36.5 y -Male BRV, PBO: 50.4%, 57.0% -White BRV, PBO: 58.2%, 57.0% -Mean duration of epilepsy BRV, PBO: 21.2 y, 22.0 y Focal seizures: 89.8% ≥2 concomitant AEDs: 82.7% Median focal seizures/week BRV, PBO: 1.42, 1.47 Key Inclusion Criteria: -Age 16-70 y -Uncontrolled seizures (h/o ≥2 focal seizures/month or ≥2 days w/ primary generalized seizures/month -≥4 focal seizures or generalized seizure (any type) days during 4-week baseline period -1-3 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	mITT: 1. n=359 2. n=121 Attrition: 1. 10% 2. 8%	Primary Endpoint: Median % reduction vs. PBO from baseline in self-reported focal seizures/week: 1. 7.3% (p=0.125) Secondary Endpoints (reported only in focal seizure mITT population only): Median % reduction in self-reported focal seizures/week from baseline: 1. 26.9% (p=0.070 vs. PBO) 2. 18.9% 95% CI not reported ≥50% responder rate (≥50% reduction from baseline in self-reported focal seizures/week): 1. 30.3% (p=0.006 vs. PBO) 2. 16.7% 95% CI not reported Seizure-free (no reported seizures of any kind) 1. 1.5% (p=0.337 vs. PBO) 2. 0% Exploratory endpoints in the generalized seizure mITT population are not reported.	NS NS 13.6%/8 NS	D/C due to AE: 1. 6.1% 2. 5.0% p-values NR SAE: 1. 5.3% 2. 7.4% p-values NR Headache: 1. 14.2% 2. 19.8% p-values NR Somnolence: 1. 11.1% 2. 4.1% p-values NR Dizziness: 1. 8.6% 2. 5.8% p-values NR Fatigue: 1. 7.8% 2. 4.1% p-values NR Psychiatric AEs: 1. 12.3% 2. 11.6% p-values NR	NA for all	**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. Missing 95% CI. Attrition Bias: High. mITT performed (≥1 dose received) and 63/543 subjects excluded from analysis. Reporting Bias: Low. Multiple subgroup analyses were prespecified. Funded by UCB Pharma. **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: Active control more appropriate; concomitant AEDs were relatively equal across all groups. Outcomes: Study was powered to assess % reduction in focal seizures versus placebo despite claim to assess safety outcomes. 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:

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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)

----------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.

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