Brand Name: Briviact

Generic Name: brivaracetam

Manufacturer[1]: UCB, Inc.

Drug Class: Antiepileptic

Uses[1, 2, 3, 4, 5]:

Labeled Uses: Adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.
Unlabeled Uses: None.

Mechanism of Action[1, 2, 3, 4, 5]: The exact mechanism the anticonvulsant activity of brivaracetam is unknown. Its anticonvulsant effect may be due to its high affinity for synaptic vesicle protein 2A (SV2A) in the brain.

Pharmacokinetics[1 ,2, 3, 4, 5]:

Absorption:

T_{max}	1 hour (0.25 to 3 hours)
V_d	0.5 L/kg
$t_{½}$	9 hours
Clearance	Not defined
Protein binding	$\leq$ 20% bound to plasma proteins
Bioavailability	Not defined

Metabolism: Brivaracetam is primarily metabolized by hydrolysis mediated by hepatic and extra-hepatic amidase. It is secondarily metabolized by hydroxylation via the CYP2C19 pathway. None of the three metabolites are pharmacologically active.

Elimination: Brivaracetam is primarily eliminated by metabolism and excretion in the urine. Over 95% of the dose is excreted in the urine within 72 hours. Less than 10% is excreted in the urine unchanged. Less than 1% is excreted in the feces.

Efficacy[7,8,9]:

Kwan P, Trinka E, Van Paesschen W, Rektor I, Johnson ME, Lu S. Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. Epilepsia. 2014; 55(1):38-46.

Study Design: Phase III, randomized, double-blind, placebo-controlled, flexible dose trial

Description of Study:

Methods: After a prospective 4-week baseline, 480 adults aged 16 to 70 with epilepsy uncontrolled by 1 to 3 antiepileptic drugs (431 with focal epilepsy and 49 with generalized epilepsy) were randomized to receive either twice daily brivaracetam or placebo. The starting dose was 20 mg/day and was increased, as needed, to 150 mg/day during an 8-week dose-finding period. Investigators slowly increased Brivaracetam at 2-week intervals based on efficacy and tolerability. Then, an 8-week stable-dose maintenance period followed. The treatment period was defined as the dose-finding period and the stable-dose maintenance period for a total of 16 weeks. Vital signs, physical and neurologic examinations, blood chemistry, hematology, urinalysis, and electroencephalography findings were recorded by the investigators. The date and number of seizures were recorded using a daily record card. Intent-to treat analysis was used to analyze the data.

Outcome Results: Ninety percent of brivaracetam and 91.7% of placebo treated patients completed the study. Sixty-six percent of brivaracetam patients and 65.3% of placebo treated patients reported adverse events. Discontinuation due to adverse effects occurred in 6.1% and 5.0% of brivaracetam and placebo treated patients, respectively. The most frequent adverse effects were headache, somnolence, and dizziness. Most efficacy endpoints for focal seizures were insignificant. During the maintenance period, brivaracetam statistically significantly improved for seizure freedom ($p = 0.003$).

Limitations: The study was sponsored by UCB Pharma, the manufacturer of brivaracetam. UCB Pharma was involved in the design, data collection, management, analysis of the data, and review of manuscript. Many of the authors have associations with UCB Pharma. The power was only calculated for the primary outcome measure, and a sufficient number of patients with generalized seizures was not enrolled to extrapolate the results to the patient population. The use of record cards could be subject to bias or human error. The flexible dosing of brivaracetam makes it difficult to determine appropriate dosing protocols. The short duration of the study and lack of statistically significant efficacy results limits current knowledge of long term effects.

Conclusion: This study confirmed good tolerability for the use of brivaracetam at individualized doses of 20 – 150 mg/day as adjunctive therapy for patients with uncontrolled epilepsy. Brivaracetam showed statistically significant efficacy in patients with focal seizures for some outcome measures. Exploratory results among patients with generalized seizures suggest that it may be useful in this population as well. This study provides support for further studies evaluating adjunctive brivaracetam for focal and generalized seizures.

Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. Epilepsia. 2014; 55(1):57-66.

Study Design: Prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed dose trial

Description of Study:

Methods: Four hundred patients who experienced eight or more partial-onset seizures, during the 8-week prospective baseline period were randomized to receive twice daily brivaracetam (5, 20, or 50 mg/day) or placebo without titration. Patients were excluded if nonmotor partial seizures was their only seizure type, they had a history of seizures occurring only in clusters, had status epilepticus or pseudo-seizures, and if they had a serious uncontrolled disease. The study started with an 8-week prospective baseline period, then a 12-week treatment period with stable dosing. The primary end-point was the partial-onset seizure frequency per week, measured by percent reduction over placebo, over 12 weeks. Intent-to-treat and modified intent-to-treat protocols were used to analyze the data.

Outcome Results: Three hundred and sixty-one patients (91.2%) completed the study. Brivaracetam reduced partial-onset seizure frequency per week was by 0.9% ($p = 0.885$) with 5 mg/day, 4.1% ($p = 0.492$) with 20 mg/day, and 12.8% ($p = 0.025$) with 50 mg /day over placebo. Brivaracetam reduced partial-onset seizure frequency per 28 days 22.0% ($p = 0.004$) with 50 mg/day over placebo but not for the other groups. Responder rate with 50 mg/day was 32.7% versus 16.7% for placebo ($p = 0.008$). Median percent reduction from baseline in partial-onset seizure frequency per week was 30.5% with 50 mg/day versus 17.8% in placebo ($p = 0.003$). The most commonly reported adverse events (BRV $\geq$ 5% versus placebo > 3%) were somnolence, dizziness, fatigue, influenza, insomnia, nasopharyngitis, vomiting, diarrhea, urinary tract infection, and nausea.

Limitations: The study was sponsored by UCB Pharma, the manufacturer of brivaracetam. UCB Pharma was involved in the design, data collection, management, analysis of the data, and review of manuscript. Many of the authors have associations with UCB Pharma. The power was only calculated for the primary outcome measure, therefore the subanalyses of seizure subtypes cannot be adequately statistically analyzed and would be difficult to extrapolate to a specific population. The short duration of the study limits current knowledge of long term effects.

Conclusion: Adjunctive brivaracetam at 50 mg/day significantly reduced seizure frequency compared to placebo. Brivaracetam was well tolerated during the study. Studies evaluating the response among seizure subtypes and the duration of long-term seizure free time would be valuable.

Klein P, Schiemann J, Sperling MR, Whitesides J, Liang W, Stalvey T, et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia. 2015; 56(12):1890-8.

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Description of Study:

Methods: Seven hundred and sixty-eight patients were randomized to receive brivaracetam 100 mg/day, brivaracetam 200 mg/day, or placebo without titration. First, patients went through an 8-week prospective baseline period, followed by a 12-week treatment period. Intent-to treat analysis was used to analyze the data.

Outcome Results: Brivaracetam 100 mg/day reduced seizure frequency over 28 days by 22.8% over placebo (95% CI 13.3-31.2%, $p = 0.001$). Brivaracetam 200 mg/day reduced seizure frequency over 28 days by 23.2% over placebo (95% CI 13.8-31.6%, $p < 0.001$). Responder rates were 21.6% for placebo, 38.9% for brivaracetam 100 mg/day (2.39, 95% CI 1.6-3.6, $p < 0.001$), and 37.8% for brivaracetam 200 mg/day (2.19, 95% CI 1.5-3.3, $p < 0.001$). Treatment-emergent adverse events occurred in 67.6% of brivaracetam patients versus 59.4% in placebo. Discontinuation rates due to adverse effects were 3.8%, 8.3%, and 6.8% for placebo, brivaracetam 100 mg/day, and brivaracetam 200 mg/day, respectively. The most common adverse effects included somnolence (7.7% vs 18.1%), dizziness (5.0% vs 12.3%), and fatigue (3.8% vs 9.5%).

Limitations: The study was sponsored by UCB Pharma, the manufacturer of brivaracetam. UCB Pharma was involved in the design, data collection, management, analysis of the data, and review of manuscript. Many of the authors have associations with UCB Pharma. Power was only calculated for the co-primary outcomes, making it difficult to extrapolate to significance of the findings of the secondary outcomes. The authors make conclusions that patients who failed levetiracetam therapy may benefit from brivaracetam, but this study was not powered to accurately and effectively evaluate that outcome. Patients recording seizure frequency and seizure type could lead to bias or human error. The short duration of the study limits current knowledge of long term effects.

Conclusion: Adjunctive brivaracetam 100 mg/day and 200 mg/day were both effective in reducing partial-onset seizures in adults and were well tolerated. Adjunctive brivaracetam 100 mg/day showed similar efficacy and a better safety profile than 200 mg/day dosing and should be considered as the initial dosing strategy of this medication in combination with their current epileptic treatment regimen.

Contraindications[1, 2, 3, 4, 5]:

Hypersensitivity to brivaracetam or any of the inactive ingredients in Briviact (bronchospasm and angioedema have occurred). [See Precautions]

Precautions[1, 2, 3, 4, 5]:

Suicidal Behavior and Ideation: May increase the risk of suicidal thoughts or behaviors. Patients taking antiepileptic drugs (AEDs) have approximately twice the risk of suicidal thinking of behavior compared to patients taking placebo as shown in an analysis of 199 placebo-controlled clinical trials of 11 different AEDs. The onset of suicidal thoughts and behaviors have been seen as early as one week after initiating drug treatment and persisted through the duration of treatment.

Neurological Adverse Reactions: Brivaracetam causes increases somnolence and fatigue in a dose-dependent manner. It also may have adverse reactions related to dizziness and disturbances in gait and coordination. The greatest risk is generally early in treatment but can occur any time.

Psychiatric Adverse Reactions: Psychiatric adverse events included non-psychotic symptoms (irritability, anxiety, nervousness, aggression, belligerence, anger, agitation, restlessness, depression, depressed mooed, tearfulness, apathy, altered mood, mood swings, affect lability, psychomotor hyperactivity, abnormal behavior, and adjustment disorder) and psychotic symptoms (psychotic disorder with hallucination, paranoia, acute psychosis, and psychotic behavior).

Hypersensitivity: Brivaracetam or any of the inactive ingredients in Briviact can cause hypersensitivity reactions that may result in bronchospasm and/or angioedema.

Withdrawal of AEDs: Brivaracetam dose should be gradually titrated down to decrease the risk of increased seizure frequency and status epilepticus. Rapid discontinuation should only be considered if a serious adverse event occurs.

Hematologic Effects: Decreased white blood cell count ($< 3.0 \times 10^9$/L) and decreased neutrophil count ($< 1.0 \times 10^9$/L) have been reported.

Adverse Effects[1, 2, 3, 4, 5]:

Occurring in >10% of patients

Nervous system disorders:

Somnolence and sedation (16%)
Dizziness (12%)

Occurring in >1% to <10% of patients

Nervous system disorders:

Fatigue (9%)
Cerebellar coordination and balance disturbances (3%)
Euphoria (≥3%)
Nystagmus (3%)

Gastrointestinal disorders:

Nausea/vomiting (5%)

Constipation (2%)
Dysgeusia (≥3%)

Psychiatric disorders:
Irritability (3%)

Hematologic abnormalities:
Decreased WBC (1.8%)

Musculoskeletal:
Ataxia (3%)

Overdose: Limited clinical experience regarding brivaracetam overdose in humans makes brivaracetam overdose difficult to define. In general, the adverse reactions associated with overdose were consistent with known adverse reactions. Vertigo, balance disorder, fatigue, nausea, diplopia, anxiety, and bradycardia have been reported following brivaracetam overdose.

Drug Interactions[1, 2, 3, 4, 5]:

Plasma concentrations of brivaracetam may be decreased:
Barbituates and combinations with barbituates
Fosphenytoin
Phenyotin

Increase exposure to the active metabolite due to brivaracetam reversibly inhibiting epoxide hydrolase:
Carbamazepine

CYP2C19 inducers may decreased brivaracetam plasma concentrations:
Enzalutamide
Hypericum
Isoniazid
Pyrazinamide
Rifampin
St. John's Wort
Tipranavir

Additive CNS depressant effects:
Ethanol
Trazodone
Tricyclic antidepressants

Plasma concentrations may be increased with concomitant treatment with brivaracetam:
Fosphenytoin

Phenytoin

Dosing/Administration[1, 2, 3, 4, 5]:

Adult Dosing

The recommended starting dose is 50 mg twice daily. Dose does not need to be titrated upon initiation. Dose can be adjust up to100 mg twice daily or down to 25 mg twice daily based on therapeutic response and patient tolerability. May be taken without regard to meals. Do not chew or crush tablets. Discontinue gradually.

Injection formulations are dosed at the same strength and frequency as the tablets and oral solution. Only use injection when oral administration is unavailable. Administer IV over 2 to 15 minutes undiluted or diluted in NS, LR, or D5W.

Pediatrics (≥4 years of age)

Safety and effectiveness of brivaracetam has not been established in patients less than 16 years of age. For adolescents 16 years of age and older, refer to adult dosing.

Geriatric

Start at the low end of the dosing range 25 mg twice daily. Insufficient evidence is available to allow adequate assessment of effectiveness in this population.

Renal impairment

Dose adjustments are not necessary for patients with renal function impairment. No current data in end-stage renal disease undergoing dialysis is available at this time, and therefore it is not recommended in this population.

Hepatic impairment

The recommended starting dose for patients with any stage of hepatic impairment is 25 mg twice daily and the recommended maximum dose is 75 mg twice daily.

Co-administration with Rifampin

Increase the dose by 100% (double the dose).

Use in Special Circumstances[1, 2, 3, 4, 5]:

Pregnancy

Pregnancy Category C. Well controlled studies in pregnant women are not currently available. Evidence of developmental toxicity was found at plasma exposures greater than clinical exposures in animal studies. Briviact should only be used in pregnancy if the potential benefits outweigh the potential risks to the fetus.

Lactation

It is unknown whether Briviact is excreted in human breast milk. Rat studies have shown excretion in milk.

CYP2C19 Poor Metabolizers

Poor metabolizers of CYP2C19 may require dose reduction.

Conclusion: Brivaracetam 50 mg/day to 200 mg/day may be beneficial in patients as adjunctive therapy for uncontrolled partial-onset seizures. It has mostly mild to moderate adverse effects, and is generally well tolerated. Uptitration is not required. Currently, no head-to-head, long-term, or single-agent studies of brivaracetam. Due to the current limitations in literature, brivaracetam should remain as adjunctive therapy alongside patients' current antiepileptic regimens. Further studies are needed to confirm if brivaracetam may have enhanced usefulness in patients who have failed levetiracetam. As with any new drug on the market, the cost is higher than current available options, potentially limiting it to a last-line therapeutic option until cost comes down, more significant benefit is shown, and long-term safety and efficacy data are available.

References:

1. Briviact [package insert]. Smyrna, GA: UCB, Inc.; 2016.
2. Brivaracetam. Lexi-Drugs [database online]. Lexi-Comp, Inc; November 22, 2016.
3. Brivaracetam. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2007. Available at: http://www.clinicalpharmacology.com. Accessed: November 22, 2016.
4. Brivaracetam. In: DISEASEDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed November 22, 2016.
5. Brivaracetam. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: November 22, 2016.
6. Tian X, Yuan M, Zhou Q, Wang X. The efficacy and safety of brivaracetam at different doses for partial-onset epilepsy: a meta-analysis of placebo-controlled studies. Expert Opin Pharmacother. 2015; 16(12):1755-67.
7. Kwan P, Trinka E, Van Paesschen W, Rektor I, Johnson ME, Lu S. Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. Epilepsia. 2014; 55(1):38-46.
8. Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. Epilepsia. 2014; 55(1):57-66.
9. Klein P, Schiemann J, Sperling MR, Whitesides J, Liang W, Stalvey T, et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia. 2015; 56(12):1890-8.

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