Drug Monograph

Drug/Drug Class:	**Briviact® (brivaracetam) tablet and suspension / Anti-epileptic**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Briviact® is available in film coated tablets in strengths of 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg of brivaracetam. It is also available in a suspension containing 10 mg brivaracetam per ml. Manufacturer: UCB, Inc., Smyrna, GA 30080.
Summary of Findings:	Briviact® reduced the seizure frequency over 28 days by approximately 23% compared with placebo and had a 50% responder rate of 37.8% to 38.9% with 100 mg and 200 mg daily doses in a large randomized, double-blind, placebo-controlled, phase 3 clinical trial. Results for the 50 mg daily dose on 7 day seizure frequency in 2 other clinical trials were conflicting. Across all 3 trials, patients with either prior or concomitant exposure to levetiracetam tended to have lower efficacy compared with levetiracetam-naïve patients. The most common adverse effects due to Briviact® are somnolence/sedation, dizziness, fatigue, and nausea/vomiting.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Non-Preferred Agent

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2,5]

A seizure is caused by abnormal electrical activity in the brain. When a seizure occurs, you may experience a variety of symptoms. Patients with partial seizures can experience motor seizures that cause change in muscle activity. Partial seizures can also be sensory seizures that cause changes in any one of the sense. They can also be autonomic seizures that cause changes in the part of the nervous system that automatically controls bodily functions. Finally, partial seizures can be psychic seizures that change how people think, feel, or experience things.

Dosage Form(s) [1]

Briviact® is available in film coated tablets in strengths of 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg of brivaracetam. It is also available in a suspension containing 10 mg brivaracetam per ml.

Manufacturer [1]

UCB, Inc., Smyrna, GA 30080.

Indication(s) [1]

Briviact® is indicated for adjunctive treatment of partial-onset seizures in patients 16 years and older with epilepsy.

Clinical Efficacy [1-4] (mechanism of action/pharmacology, comparative efficacy)

The exact mechanism by which Briviact® exerts its anticonvulsant activity is unknown. Briviact® has a high and selective affinity for synaptic vesicle protein 2A in the brain, which may contribute to the anticonvulsant effect.

Pharmacokinetics:

	Briviact®
Protein binding	≤ 20%
Metabolism	Liver, via hydrolysis and hydroxylation (CYP2C19) to inactive metabolites
Excretion	Feces, < 1% Urine, > 95% (<10% unchanged)
Half-life	9 hours
Volume of distribution	0.5 L/kg

Compared with placebo, Briviact® reduced seizure frequency when used as add-on therapy for partial-onset seizures.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial (N=760)
INCLUSION CRITERIA	Patients 16 to 80 years of age with uncontrolled partial-onset seizures (ie, at least 8 during the 8-week baseline period) despite treatment with 1 or 2 concomitant antiepileptic agents.
EXCLUSION CRITERIA	Concomitant treatment with levetiracetam or history of status epilepticus in the prior year.
TREATMENT REGIMEN	Patients were randomized to Briviact® 100 mg daily, 200 mg daily, or placebo. Doses were administered in 2 equally divided doses per day.
RESULTS	At baseline, patients had a mean duration of epilepsy of 22.8 years and 71.3% were taking 2 concomitant antiepileptic drugs, with carbamazepine as the most common in 37% of patients. A significant reduction in the seizure frequency over 28 days compared with placebo was achieved both with Briviact® 100 mg/day (22.8%) and with Briviact® 200 mg/day (23.2%). A significantly greater proportion of Briviact®-treated patients experienced at least a 50% response from baseline (100 mg/day, 38.9%; 200 mg/day, 37.8%) compared with placebo (21.6%). Patients with prior exposure to levetiracetam (about 54%) had lower efficacy compared with levetiracetam-naïve patients.
SAFETY	The most common adverse effects reported in the Briviact® groups consisted of somnolence, dizziness, and fatigue.

Contraindications (1)

- Hypersensitivity to Briviact® or any inactive ingredients

Warnings and Precautions (1)

- Hepatic impairment; dose adjustment is recommended for all stages
- Hypersensitivity reactions have occurred, including bronchospasm and angioedema; discontinue if condition occurs
- Neurologic reactions have been reported, including somnolence, fatigue, dizziness, and disturbance in coordination; avoidance of driving or operating machinery until drug effects are realized and monitoring recommended
- Suicidal behavior and ideation may occur; evaluation of risk versus benefit prior to use and monitoring recommended
- Nonpsychotic and psychotic symptoms have been reported, including anxiety, aggression, anger, agitation, depression, apathy, altered mood, affect lability,

psychomotor hyperactivity, adjustment disorder, psychotic disorder, hallucinations, paranoia, and acute psychosis

- ESRD undergoing dialysis; use not recommended
- Gradual withdrawal of therapy is recommended due to risk of increased seizure frequency and status epilepticus

Adverse Effects [1]

Most common, ≥ 2 % higher than placebo	Briviact® (n=803)	Placebo (n=459)
Somnolence/sedation	16%	8%
Dizziness	12%	7%
Fatigue	9%	4%
Nausea/vomiting	5%	3%
Cerebellar coordination/ balance disturbances	3%	1%
Irritability	3%	1%

Drug Interactions [1]

- Rifampin
- Carbamazepine
- Phenytoin
- CYP2C19 inhibitors

Dosage and Administration [1]

The recommended initial dose for Briviact® is 50 mg twice daily. The dosage may be adjusted down to 25 mg twice daily or up to 100 mg twice daily depending on clinical response and tolerability. Dosage adjustments are necessary with any stage of hepatic impairment and concomitant rifampin. Avoid abrupt withdrawal when discontinuing.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST/ MONTH
Brivaracetam	Briviact	UCB	10 mg tab	1 tablet twice daily	$909.60*
			25 mg tab	1 tablet twice daily	$909.60*

			50 mg tab	1 tablet twice daily	$909.60*
			75 mg tab	1 tablet twice daily	$909.60*
			100 mg tab	1 tablet twice daily	$909.60*
			10 mg/ml solution	5 ml twice daily	$909.60*
Levetiracetam	Keppra	UCB	250 mg tab	1 tablet twice daily	$5.40**
			500 mg tab	1 tablet twice daily	$8.40**
			750 mg tab	1 tablet twice daily	$12.60**
			1000 mg tab	1 tablet twice daily	$32.40**
			100 mg/ml solution	5 ml twice daily	$18.00**

* Wholesale Acquisition Cost

** Maximum Allowable Cost

Conclusion

Briviact® is an antiepileptic agent approved for the adjunctive treatment of partial-onset seizures in patients with epilepsy. Briviact® does not require a gradual dose titration when initiating therapy. Brivaracetam reduced the seizure frequency over 28 days by approximately 23% compared with placebo and had a 50% responder rate of 37.8% to 38.9% with 100 mg and 200 mg daily doses in a large randomized, double-blind, placebo-controlled, phase 3 clinical trial. Patients with either prior or concomitant exposure to levetiracetam tended to have lower efficacy compared with levetiracetam-naïve patients. The most common adverse effects due to Briviact® are somnolence/sedation, dizziness, fatigue, and nausea/vomiting.

Recommendation

The Division recommends adding this drug to the current 15 day quantity limitation fiscal edit and to the current psychotropic polypharmacy clinical edit.

References

1. Product Information: Briviact™, brivaracetam injection, oral solution, tablets. UCB, Inc, Smyrna, GA, 02/2016.
2. Klein P, Schiemann J, Sperling M 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):1890-1898.
3. Biton V, Berkovic S, bou-Khalil B et al: 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.
4. Ryvlin P, Werhahn K, Blaszczyk B et al: Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia 2014; 55(1):47-56.

5. Simple Partial Seizures. Retrieved 8/22/16 from http://www.epilepsy.com/learn/types-seizures/simple-partial-seizures

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Date: August 22, 2016

