BRIVIACT® (brivaracetam) CV Medicaid Testimony (Print)

This Testimony will discuss unmet treatment needs in epilepsy, its socioeconomic and cost burden, and UCB's product BRIVIACT.

- In the U.S., 1 in 26 patients will develop epilepsy in their lifetime and 3.4 million Americans are living with epilepsy.[1,2]
- Epilepsy is a complex and heterogeneous disease with numerous causes, seizure types, and serious comorbidities. In addition, seizures have a range of severities, and the same seizure type may present differently in individual patients.[3,4]
- Drug therapy for each epilepsy patient needs to be individuated to reach optimal treatment.[5-8]
- Epilepsy is not only associated with seizures, but also with increased mortality and morbidity. Epilepsy has a 3-fold increase in mortality compared to the general population.[9]

Despite the availability of over 25 antiepileptic drugs (AEDs), unmet treatment needs remain. More than 30% of patients continue to experience seizures and are considered refractory to therapy.[10]

- Treatment of refractory epilepsy relies on combining a broad range of AEDs to obtain the best seizure control with as few side effects as possible for any one individual; therefore, there is a need for numerous AED options.[5-8]
- Unlike other diseases, interchangeability between drug treatment leads to differences in patient response even when treating the same seizure type. Within the same AED mechanistic class, interchangeability between AEDs can also lead to variability in patient response.[5-8]
- As a result, numerous AED options with diverse mechanisms of action (MOAs) are necessary and can be used in combination to target various pathways. In addition, AEDs within the same mechanistic class are needed to optimize seizure control in any given patient.[5-8]
- Tolerability to any given AED or combination of AEDs also varies widely by individual, and intolerability to AEDs persists as a major treatment challenge. Approximately 50% of all treated epilepsy patients experience mild to moderately severe adverse events.[11,12]
- Drug interactions and the pharmacokinetic (PK) profile are also common considerations when selecting an AED. Up to 84% of epilepsy patients have at least one comorbidity leading to the potential for numerous drug interactions.[13]
- AED therapy is therefore often selected based on the drug's tolerability profile, drug interaction profile, MOA, and ability to treat specific seizure type(s).[5-8]

Epilepsy results in a substantial socioeconomic and cost burden.[14]

- Data from 1996-2004 estimates the national economic impact of epilepsy medical expenditures and informal care to be $9.6 billion annually in the U.S.[15]
- The economic impact of informal care by caregivers of epilepsy patients outside of their household has been estimated to be $99.6 million annually in the U.S.[15]
- Hospitalizations are a major contributor to the cost burden of epilepsy with approximately 1.4 million hospital stays linked to epilepsy or convulsions in 2005. Of these stays that had epilepsy or convulsions as the principal reason for hospitalization nearly $1.8 billion in hospital costs was spent.[16]
- Various retrospective studies have identified uncontrolled seizures, breakthrough seizures, increased seizure severity, and medication non-adherence as primary patient and disease characteristics that contribute to hospitalizations and emergency room (ER) visits related to epilepsy.[17,18]
- Claims database studies have established that patients with uncontrolled seizures incur an additional cost burden compared to those with stable seizure control.[14,19] In a latest study evaluating uncontrolled patients with a hospital visit, patients incur an additional 2.5 times higher cost burden ($7,619) within 6 months compared to controlled patients.[19]
- A recent large claims database study across the U.S. examined healthcare factors associated with decreased hospitalizations related to epilepsy. Access to AEDs, access to specialty clinicians (neurologists), and a medication change at the time of an epilepsy-related hospital encounter were detected as major healthcare factors that can reduce hospitalizations in epilepsy.[20]
- Choice of AED can also add to healthcare utilization.[21] One recent retrospective U.S. chart review analysis of 811 epilepsy patients indicates that the time to reach a maintenance dose of

AED (the titration period) may be associated with increased epilepsy healthcare resource use and costs. Healthcare resource use cost was increased by 47% during the titration phase compared to the 6 month post-maintenance period.[22]

- In the U.S., epilepsy patients face employment challenges. The unemployment rates for adults with epilepsy are 2 times higher than the national average.[23] The rate is even higher in adults with uncontrolled seizures, approaching an unemployment rate of 50%.[24]
- Underemployment is also a widespread problem for people with epilepsy.[25]
- People living with epilepsy also face daily challenges due to the loss of driving privileges.[26]

For the past 15 years, UCB has been focused on developing new medicines and solutions to address the unmet needs for people with epilepsy.

- Currently, UCB's ongoing AED clinical development program is aimed at addressing unmet needs of people with epilepsy.[27]
- 100% of BRIVIACT utilization is in patients with epilepsy.[28]
- UCB remains committed to epilepsy patients and continues to evaluate new treatment options for epilepsy.[27]

BRIVIACT is indicated for the treatment of partial-onset seizures in patients 4 years of age and older and is a Schedule V controlled substance. As the safety of BRIVIACT injection has not been established in pediatric patients, BRIVIACT injection is indicated for the treatment of partial-onset seizures in adults (16 years of age and older). In May 2018, BRIVIACT's indication was updated within the Prescribing Information.[29]

- BRIVIACT was rationally designed to be a distinct member of the synaptic vesicle protein 2A (SV2A) class.[30]
- BRIVIACT was discovered from a rational drug discovery screening project of 12,000 racetam derivatives to identify selective, high-affinity SV2A ligands.[31]
- BRIVIACT displays a high and selective affinity for SV2A in the brain, which may contribute to the anticonvulsant effect. The precise mechanism by which BRIVIACT exerts its anticonvulsant activity is not known. [29]
- *In vitro* studies have shown that BRIVIACT has a 15- to 30-fold higher affinity to SV2A compared to levetiracetam (LEV) and that BRIVIACT lacks activity at high voltage activated calcium channels and AMPA receptors.[32-35] The clinical significance of these *in vitro* data is unknown.

BRIVIACT has demonstrated efficacy in reducing seizure frequency in three placebo-controlled adjunctive studies of 1,550 adult patients with uncontrolled partial-onset seizures.[29]

- In the patient population studied, 72% to 86% were taking two or more concomitant AEDs, with a mean duration of epilepsy of 23 years and a baseline median seizure frequency of 9 partial-onset seizures per 28 days.[29]

In a pooled analysis of the three pivotal studies, reduction over placebo in baseline-adjusted partial-onset seizure frequency per 28 days was 19.5%, 24.4%, and 24.0% for BRIVIACT doses of 50, 100, and 200 mg/day, respectively.[36]

- In Study 3, complete seizure freedom was achieved in 5.2% and 4.0% of uncontrolled subjects treated with BRIVIACT 100 and 200 mg/day, compared to 0.8% in placebo.[37]
- In Studies 1 and 2, approximately 20% of patients were on concomitant LEV. Although the numbers were limited, BRIVIACT provided no added benefit when it was added to LEV.[29]
- All three studies included patients with prior LEV exposure. In Study 3, 54% of patients had prior LEV exposure and efficacy in prior LEV subjects was examined with a pre-specified analysis. Efficacy over placebo was observed among patients with prior LEV exposure taking BRIVIACT.[37]

The pediatric indication for BRIVIACT was based on FDA acceptance of extrapolated adult partial-onset seizure efficacy data to pediatrics down to 4 years of age, given that certain conditions are met.

- The safety and effectiveness of BRIVIACT in pediatric patients 4 to 16 years of age have been established by evidence from adequate and well-controlled studies of BRIVIACT in adults with

partial-onset seizures, pharmacokinetic data from both adult and pediatric populations, and safety data in 149 pediatric patients.[29]

BRIVIACT is associated with important warnings and precautions including suicidal behavior and ideation, neurological adverse reactions, psychiatric adverse reactions, and hypersensitivity reactions (bronchospasm and angioedema). BRIVIACT is contraindicated in patients with a prior hypersensitivity reaction to brivaracetam or any of the inactive ingredients. The most common adverse reactions are somnolence and sedation, dizziness, fatigue, and nausea and vomiting. Most common adverse reactions in pediatric patients are similar to those seen in adult patients.[29]

- There was no apparent dose-dependent increase in adverse reactions with the exception of somnolence and sedation.[29]
- Long-term BRIVIACT safety data in patients with partial-onset seizures reflects 7,879 patient-years of exposure over 11 years. BRIVIACT was generally well tolerated.[38]

Gradual dose escalation is not required with BRIVIACT. A therapeutic dose can be initiated on the first day of treatment. Dose adjustments with BRIVIACT are recommended for patients with all stages of hepatic impairment and when co-administered with rifampin.[29]

- Initiating a therapeutic dose on the first day of treatment[29] is different from many common AEDs that may take 7-126 days to reach a target dose.[39-45]
- No dose adjustments are required when co-administered with other AEDs; however, interactions with carbamazepine and phenytoin may be clinically relevant.[29]
- BRIVIACT is extensively metabolized, which is distinct from the metabolism of LEV.[35] Its metabolism is primarily mediated by hepatic and extra-hepatic amidase and secondarily mediated by CYP2C19 hydroxylation and CYP2C9 hydrolysis.[29]
- Additionally, BRIVIACT is highly permeable and rapidly distributed to most tissues.[29]

BRIVIACT is available in three formulations (tablets, oral solution, and injection) for use in adults and in two formulations (tablets and oral solution) for use in children 4 to less than 16 years of age.[29] No dosage adjustments are necessary when switching between formulations, allowing for uninterrupted therapy between outpatient and inpatient care settings.[29]

- BRIVIACT is an option for those patients who are having uncontrolled partial-onset seizures.[29]

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