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BRIVIACT-A REVIEW

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Abstract:

BRIVIACT (brivaracetam) is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy. Approximately one third of patients with epilepsy fail to respond to existing medications. Brivaracetam is a novel high affinity SV2A ligand with approximately 20-fold higher affinity for SV2A protein than levetiracetam. Its effectiveness in reducing the frequency of seizures was demonstrated in 3 placebo-controlled trials in 1550 patients who were also taking other antiepileptic drugs (AEDs) concomitantly. In January 2016, the European Commission granted the marketing authorization for BRIVIACT® as an adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent patients from 16 years of age with epilepsy.

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INTRODUCTION:

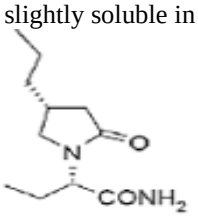
Epilepsy is a brain disorder that causes people to have recurring seizures. A seizure is an episode, usually of relatively short duration, of abnormal brain activity. Seizures can cause a variety of symptoms, including uncontrolled movements or spasms, abnormal thinking and behavior, and abnormal sensations. Muscle spasms can be violent, and loss of consciousness can occur. Seizures occur when clusters of nerve cells (neurons) in the brain undergo uncontrolled activation. A partial onset seizure begins in a limited area of the brain.

BRIVIACT® is a new molecular entity that was rationally designed and developed by UCB. **It was approved by the FDA in February 2016.**

Briviact is specifically indicated as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy. It displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the anticonvulsant effect. However, the precise mechanism by which Briviact exerts its anticonvulsant activity is not known.

DESCRIPTION:

The chemical name of BRIVIACT (brivaracetam) is (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl] butanamide. Its molecular formula is C11H20N2O2 and its molecular weight is 212.29. The chemical structure is: Brivaracetam is a white to off-white crystalline powder. It is very soluble in water, buffer (pH 1.2, 4.5, and 7.4), ethanol, methanol, and glacial acetic acid. It is freely soluble in acetonitrile and acetone and soluble in toluene. It is very slightly soluble in n-hexane.



Briviact is supplied in three formulations: Tablet, oral solution and injection for intravenous administration. The recommended starting dosage is 50 mg twice daily (100 mg per day). 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).

Briviact must be dispensed with a Medication Guide for patients, which provides important information about the medication's use and risks. As is true for all drugs that treat epilepsy, the most serious risks include thoughts about suicide, attempts to commit suicide, feelings of agitation, new or worsening depression, aggression, and panic attacks. Rarely, patients may exhibit an allergic reaction associated with swelling of the lips, eyelids, or tongue with or without difficulty breathing.

CLINICAL TRIALS:

In all controlled and uncontrolled trials performed in adult epilepsy patients, BRIVIACT was administered as adjunctive therapy to 2437 patients. Of these patients, 1929 were treated for at least 6 months, 1500 for at least 12 months, 1056 for at least 24 months, and 758 for at least 36 months. A total of 1558 patients (1099 patients treated with BRIVIACT and 459 patients treated with placebo) constituted the safety population in the pooled analysis of Phase 3 placebo-controlled studies in patients with partial-onset seizures (Studies 1, 2, and 3). The adverse reactions presented in Table 2 are based on this safety population; the median length of treatment in these studies was 12 weeks. Of the patients in those studies, approximately 51% were male, 74% were Caucasian, and the mean age was 38 years.

In the Phase 3 controlled epilepsy studies, adverse events occurred in 68% of patients treated with BRIVIACT and 62% treated with placebo. The most common adverse reactions occurring at a frequency of at least 5% in patients treated with BRIVIACT doses of at least 50 mg/day and greater than placebo were somnolence and sedation (16%), dizziness (12%), fatigue (9%), and nausea and vomiting symptoms (5%). The discontinuation rates due to adverse events were 5%, 8%, and 7% for patients randomized to receive BRIVIACT at the recommended doses of 50 mg, 100 mg, and 200 mg/day, respectively, compared to 4% in patients randomized to receive placebo.

Studies 1 and 2

- The primary efficacy analysis for Studies 1 and 2 was based on partial-onset seizure frequency during the treatment period adjusted over 7 days
- A sequential testing procedure, which required statistical significance at the 0.05 level in both studies, was used to evaluate BRIVIACT doses
- In Study 1, statistically significant treatment effect was not observed for the 50 mg/day dose; the 100 mg/day dose was nominally significant
- In Study 2, the 50 mg/day dose showed a statistically significant treatment effect

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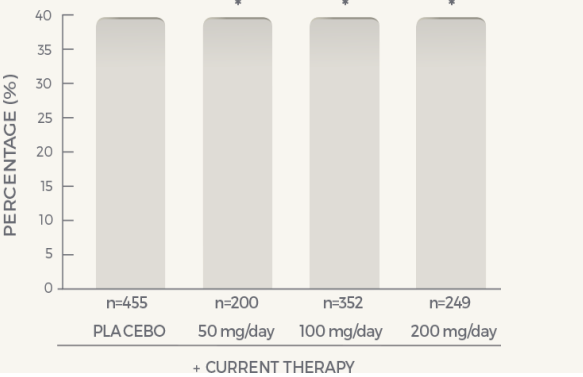
Study 3:

- The primary efficacy analysis for Study 3 was based on partial-onset seizure frequency during the treatment period adjusted over 28 days

- The 100 mg/day and 200 mg/day doses showed a statistically significant treatment effect

The most common adverse reactions (at least 5% for BRIVIACT and at least 2% more frequently than

placebo) are somnolence and sedation, dizziness, fatigue, and nausea and vomiting symptoms



PHARMACOKINETICS:

BRIVIACT tablets, oral solution, and injection can be used interchangeably. Brivaracetam exhibits linear and time-independent pharmacokinetics at the approved doses.

Absorption

Brivaracetam is highly permeable and is rapidly and almost completely absorbed after oral administration. The median T max for tablets taken without food is 1 hour (range 0.25 to 3 hours). Co-administration with a high-fat meal slowed absorption, but the extent of absorption remained unchanged.

Distribution

Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of distribution is 0.5 L/kg, a value close to that of the total body water. Brivaracetam is rapidly and evenly distributed in most tissues.

Metabolism

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxyl metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amides'. The hydroxylation pathway is mediated primarily by CYP2C19. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. An additional hydroxyl acid metabolite is created by hydrolysis of the amide moiety on the hydroxyl metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). None of the 3 metabolites are pharmacologically active.

Excretion

Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, including metabolites, is excreted in the urine within 72 hours after intake. Fecal excretion accounts for less than 1% of the dose. Less than 10% of the dose is excreted unchanged in the urine. Thirty-four percent of the dose is excreted as the carboxylic acid metabolite in urine. The terminal plasma half-life (t1/2) is approximately 9 hours.

Pregnancy

Brivaracetam is classified in Pregnancy Category C. and it should be used only during pregnancy if the anticipated benefit justifies the risk to the unborn child. It is not known whether the drug is accreted in human milk and a decision should be made whether to discontinue nursing or not we the drug. The effectiveness and safety of brivaracetam in patients younger than 16 years have not been established.

Adverse events

The adverse events reported most often in the clinical studies of brivaracetam include somnolence and sedation (16%). dizziness (12%). fatigue (9%). and nausea or vomiting (5%). The risk of sedation and other neurologic adverse events is greatest early in treatment, but can occur at any time. Patients should be cautioned not to drive or operate machinery until they have gained sufficient experience with the medication to determine whether it adversely affects their ability to participate in these activities. The concurrent use of other central nervous system depressants including alcoholic beverages should be expected to increase the likelihood of adverse neurologic events.

There have been infrequent reports of hypersensitivity reactions (e.g. Bronchospasm, angioedema) in patients treated with brivaracetam, and the drug should be discontinued if such events occur. The use of brivaracetam is contraindicated in patients known to be hypersensitive to the drug or any of the inactive ingredients in the formulation.

WARNINGS AND PRECAUTIONS:

- Suicidal Behavior and Ideation: Antiepileptic drugs, including BRIVIACT, increase the risk of suicidal behavior and ideation. Monitor patients taking BRIVIACT for the emergence or worsening of depression; unusual changes in mood or behavior; or suicidal thoughts, behavior, or self-harm. Advise patients, their caregivers, and/or families to be alert for these behavioral changes and report them immediately to a healthcare provider.
- Neurological Adverse Reactions: BRIVIACT causes somnolence, fatigue, dizziness, and disturbance in coordination. Somnolence and fatigue-related adverse reactions were reported in 25% of patients taking at least 50 mg per day of BRIVIACT compared to 14% of patients taking

placebo. Dizziness and disturbance in gait and coordination were reported in 16% of patients taking at least 50 mg per day of BRIVIACT compared to 10% of patients taking placebo. The risk is greatest early in treatment but can occur at any time. Monitor patients for these signs and symptoms and advise them not to drive or operate machinery until they have gained sufficient experience on BRIVIACT.

- Psychiatric Adverse Reactions: BRIVIACT causes psychiatric adverse reactions, including non-psychotic and psychotic symptoms. These events were reported in approximately 13% of patients taking at least 50 mg per day of BRIVIACT compared to 8% of patients taking placebo. A total of 1.7% of adult patients taking BRIVIACT discontinued treatment due to psychiatric reactions compared to 1.3% of patients taking placebo. Advise patients to report these symptoms immediately to a healthcare provider.
- Hypersensitivity: BRIVIACT can cause hypersensitivity reactions. Bronchospasm and angioedema have been reported. Discontinue BRIVIACT if a patient develops a hypersensitivity reaction after treatment. BRIVIACT is contraindicated in patients with a prior hypersensitivity reaction to brivaracetam or any of the inactive ingredients.
- Withdrawal of Antiepileptic Drugs: As with all antiepileptic drugs, BRIVIACT should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

DRUG INTERACTIONS

- Rifampin- Co-administration with rifampin decreases BRIVIACT plasma concentrations likely because of CYP2C19 induction. Prescribers should increase the BRIVIACT dose by up to 100% (i.e., double the dosage) in patients while receiving concomitant treatment with rifampin.
- Carbamazepine- Co-administration with carbamazepine may increase exposure to carbamazepine-epoxide, the active metabolite of carbamazepine. Though available data did not reveal any safety concerns, if tolerability issues arise when co-administered, carbamazepine dose reduction should be considered.
- Phenytoin- Because BRIVIACT can increase plasma concentrations of phenytoin, phenytoin levels should be monitored in patients when concomitant BRIVIACT is added to or discontinued from ongoing phenytoin therapy
- Levetiracetam- BRIVIACT provided no added therapeutic benefit to levetiracetam when the two drugs were co-administered.

PATIENT COUNSELING INFORMATION:

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- ***Suicidal Behavior and Ideation*** -Counsel patients, their caregivers, and/or families that antiepileptic drugs, including BRIVIACT, may increase the risk of suicidal thoughts and behavior, and advise patients to be alert for the emergence or worsening of symptoms of depression; unusual changes in mood or behavior; or suicidal thoughts, behavior, or thoughts about self-harm. Advise patients, their caregivers, and/or families to report behaviors of concern immediately to a healthcare provider.

- ***Neurological Adverse Reactions*** Counsel patients that BRIVIACT causes somnolence, fatigue, dizziness, and gait disturbance. These adverse reactions, if observed, are more likely to occur early in treatment but can occur at any time. Advise patients not to drive or operate machinery until they have gained sufficient experience on BRIVIACT to gauge whether it adversely affects their ability to drive or operate machinery.

- ***Psychiatric Adverse Reactions*** Advise patients that BRIVIACT causes changes in behavior (e.g., aggression, agitation, anger, anxiety, and irritability) and psychotic symptoms. Instruct patients to report these symptoms immediately to their healthcare provider [see Warnings and Precautions (5.3)].

- ***Hypersensitivity:*** Bronchospasm and Angioedema Advise patients that symptoms of hypersensitivity including bronchospasm and angioedema can occur with BRIVIACT. Instruct them to seek immediate medical care should they experience signs and symptoms of hypersensitivity.

- ***Withdrawal of Antiepileptic*** Drugs Advise patients not to discontinue use of BRIVIACT without consulting with their healthcare provider. BRIVIACT should normally be gradually withdrawn to reduce

the potential for increased seizure frequency and Status Epilepticus.

- ***Pregnancy Advise*** patients to notify their healthcare provider if they become pregnant or intend to become pregnant during BRIVIACT therapy.

- ***Dosing Instructions*** Counsel patients that BRIVIACT may be taken with or without food. Instruct patients that BRIVIACT tablets should be swallowed whole with liquid and not chewed or crushed. Advise patients that the dosage of BRIVIACT oral solution should be measured using a calibrated measuring device and not a household teaspoon. Instruct patients to discard any unused BRIVIACT oral solution after 5 months of first opening the bottle.

CONCLUSION:

BRV is a rationally developed third-generation antiepileptic drug with higher binding to SV2A and additional mechanisms of actions. Animal studies are promising regarding its efficacy in a wide spectrum of epilepsy models. Clinical studies have shown good tolerability at dosages of up to 50 mg/day

Brivaracetam is included in Schedule V under the provisions of the Controlled Substances Act.

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