

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205836Orig1s000**

**205837Orig1s000**

**205838Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION**  
**REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 22, 2016

Reviewer(s): Erin Hachey, Pharm.D.  
Division of Risk Management (DRISK)

Acting Team Leader: Jamie Wilkins Parker, Pharm.D., DRISK

Division Director: Cynthia LaCivita, Pharm.D., DRISK

Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Briviact (brivaracetam)

Therapeutic Class: Antiepileptic, 2-pyrrolidone derivative

Formulations: Film-coated tablet, oral solution, and solution for injection

Dosing Regimen: 25 mg twice daily to 100 mg twice daily

Proposed Indication(s): Adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy

Application Type/Number: NDAs 205836, 205837, and 205838

Applicant/Sponsor: UCB, Inc.

OSE RCM #: 2014-2449, 2014-2524, and 2015-586

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# 1 Introduction

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME) Briviact (brivaracetam), to ensure the benefits outweigh the risks. A new drug application (NDA 205836) for brivaracetam tablets was received by the Division of Neurology Products from UCB, Inc. (UCB) on November 24, 2014. Also submitted, in parallel, were NDAs 205837 and 205838, for the approval to market brivaracetam injection and oral solution, respectively. The Applicant did not submit a REMS with these applications, but did submit a proposed risk management plan with each NDA, which includes routine pharmacovigilance, a pregnancy registry, and recommendations for labeling.

## 2 Background

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### 2.1 PRODUCT INFORMATION

The new molecular entity (NME), brivaracetam, is a 2-pyrrolidone derivative that displays a high and selective affinity for brain-specific binding site synaptic vesicle protein 2A (SV2A). The Applicant reports that this appears to be the primary target for brivaracetam's pharmacological activity, though the precise mechanism by which it exerts its antiepileptic effects has not yet been fully established. The proposed indication of brivaracetam is as adjunctive therapy in the treatment of partial onset seizures (POS) in patients 16 years of age and older with epilepsy.

The proposed dosage forms of brivaracetam include oral tablets, oral solution, and injection for intravenous (IV) use. Tablets would be available in 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg strengths. Oral solution would be available in a 10 mg/mL solution. Injection would be available in a 50 mg/5 mL solution, supplied as <sup>(b)</sup><sub>(4)</sub> mL single use vials. The injection form may be used when oral administration is temporarily not feasible.

The proposed recommended starting dosage is 50 mg twice daily. Based on individual patient response, the dosage may be adjusted between 25 mg twice daily and 100 mg twice daily. Initial titration to an effective dosage is not required for tolerability. It may be administered as a bolus injection or as a 15-minute IV infusion. When switching between oral and intravenous administration of brivaracetam, the total daily dose and frequency of administration should be maintained. Brivaracetam may be administered in both inpatient and outpatient settings; however, the clinical study experience of IV brivaracetam is limited to four days of consecutive treatment.

The duration of treatment for seizure disorder is long-term, and brivaracetam has extensive exposure, which includes data up to 8 years. Brivaracetam is currently not marketed outside of the United States; however, UCB submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) at the same time the three NDAs were submitted to the FDA.

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDAs 205836, 205837, and 205838 relevant to this review:

- November 20, 2014: The Agency received two original NDA submissions from UCB for brivaracetam solution for injection and brivaracetam oral solution. The Applicant did not submit a proposed REMS.
- November 24, 2014: The Agency received an original NDA submission for brivaracetam oral tablets. The Applicant did not submit a proposed REMS.
- March 17, 2015: The 120-day Safety Update was submitted to the Agency (Seq. 0009).
- May 6, 2015: The Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that, based on the currently available data, there were no safety issues that would require a REMS for brivaracetam.
- June 22, 2015: The Agency sent an information request (IR) to the Applicant to assist with a full evaluation of the safety datasets, and, more specifically, requested analyses of hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) using actual laboratory data and vital signs, rather than the MedDRA-preferred term, pyrexia.
- July 29, 2015: The Late-cycle meeting was held between the Agency and the Applicant.
- August 20, 2015: Upon receipt of additional safety data sets and tables, the Agency issued a major amendment acknowledgment letter to the Applicant in response to the August 11, 2015 submission.

## 3 Medical Condition and Treatment Options

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### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Epilepsy is a clinical phenomenon in which a person has recurrent seizures due to a chronic underlying process. Approximately 1-3% of people in the United States will develop epilepsy over the course of their lives. The incidence of epilepsy is somewhat higher for men than women. Patients with epilepsy have approximately 2-3 times the risk of death from any cause, compared with persons without epilepsy. Seizures may cause significant trauma, drowning, or accidental injury. Many of the deaths of persons with epilepsy are directly related to seizures, accidents and injuries arising from seizures, or the underlying condition resulting in seizures. In addition, uncontrolled seizures can result in patients losing their jobs or driving privileges.<sup>1</sup>

The three main types of seizures in patients with epilepsy include partial, generalized, and unclassified. Although the population study numbers do not specifically refer to partial seizures, it is accepted as the

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<sup>1</sup> Talati R, Scholle JM, Phung OJ, Baker WL, Baker EL, Ashaye A, Kluger J, Quercia R, Mather J, Giovanale S, Coleman CI, White CM. Effectiveness and Safety of Antiepileptic Medications in Patients with Epilepsy. Comparative

most common seizure type in children and adults. Overall, more than half of seizures in the epilepsy population are partial. This applies across all age groups.<sup>2,3</sup> Despite the development of more than 10 new antiepileptic drugs (AED) since 1992, one-third of epilepsy cases are not properly controlled.

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

According to the Applicant, 30-40% of epilepsy patients continue to experience seizures, despite treatment with several different antiepileptic drug (AED) monotherapies or combinations of two or more AEDs. Thus, there is an unmet medical need for novel AEDs.

Brivaracetam is a substituted analog of levetiracetam. Levetiracetam, which is marketed as Keppra and generic drugs, was approved in 1999 as adjunct therapy in the treatment of partial onset seizures in adults with epilepsy. Keppra does not have a REMS or boxed warning, but the most recently approved (March 2015) labeling includes the following Warnings and Precautions:

- Behavioral abnormalities (5.1)
- Suicidal behavior and ideation (5.2)
- Somnolence and fatigue (5.3)
- Withdrawal seizures (5.4)

The Applicant claims that, in contrast to levetiracetam, brivaracetam displays a markedly higher selectivity and affinity for SV2A, and brivaracetam’s mode of action does not involve inhibition of high-

Carbamazepine	Levetiracetam	Tiagabine
Eslicarbazepine	Oxcarbazepine	Topiramate
Ezogabine	Perampanel	Valproic Acid
Felbamate	Phenobarbital	Vigabatrin
Gabapentin	Phenytoin	Zonisamide
Lacosamide	Pregabalin	
Lamotrigine	Primidone	

Source: Dinsmore S. Division of Neurology Products, Clinical Efficacy Review of Brivaracetam, dated January 15, 2016.

<sup>2</sup> Effectiveness Review No. 40. AHRQ Publication No. 11(12)-EHC082-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2011. [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

<sup>3</sup> Berg, AT et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010;51:676-685.

voltage activated calcium currents and AMPA-gated currents.

## 4 Benefit Assessment

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### 4.1 EFFICACY OF BRIVARACETAM FOR PARTIAL ONSET SEIZURES (POS)

The population in the brivaracetam clinical studies belongs to what has been called “treatment non-responders” or “refractory.” Some experts define a patient as having refractory seizures if treatment fails to achieve seizure freedom for 12 months or more, for whatever reason.<sup>4</sup> The generally accepted definition of refractory seizures is failure of two or more drugs, and occurrence of one or more seizures per month, over 18 months.<sup>5</sup>

#### *Brivaracetam Oral Tablets NDA 205836*

The efficacy and safety of brivaracetam oral tablets for the adjunctive treatment of partial onset seizures POS in subjects 16 years of age and older was demonstrated in three pivotal Phase 3 studies (1252, 1253, and 1358). All three studies evaluated the efficacy and safety of oral brivaracetam (tablets) in subjects taking one or two AEDs with or without secondary generalization. The three studies were similar in design: multi-center, randomized, double-blind, and placebo-controlled. Each of these studies had the same primary efficacy endpoint: the reduction in POS frequency over the placebo group. A 20% reduction over placebo reflects a clinically relevant reduction, and all three studies were powered to detect a 20% reduction over placebo.

Pivotal Study 1358 randomized 768 subjects to receive placebo (n=259), brivaracetam 100 mg /day (n=252), or brivaracetam 200 mg/day (n=249), over a 12-week treatment period. Subjects receiving concomitant levetiracetam and those who had used levetiracetam within 90 days prior to study entry were excluded, due to the drug’s mechanism of action, which overlaps that of brivaracetam. A total of 696 subjects (90.6%) completed the study. The brivaracetam 100 mg/day group demonstrated a 22.8% ( $p < 0.001$ ) reduction in POS frequency, and the brivaracetam 200 mg/day group demonstrated a 23.2% ( $p < 0.001$ ) reduction.

Pivotal Study 1252 included 398 patients randomized to a fixed-dose of placebo (n=100) or brivaracetam 20 mg/day (n=99), 50 mg/day (n=99), or 100 mg/day (n=100), over a 12-week treatment period. The number of subjects using concomitant levetiracetam was limited to 20% of the total study population due to the possibility of a pharmacodynamics interaction between levetiracetam and brivaracetam, due to their overlapping mechanisms of action. For the primary endpoint analysis, the reduction in POS frequency per week over placebo was 6.5% in the brivaracetam 50 mg/day ( $p=0.261$ ) group and 11.7%

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<sup>4</sup> P. Kwan and M.J. Brodie, Early identification of refractory epilepsy, *N Engl J Med* 342 (2000), pp. 314–39.

<sup>5</sup> A.T. Berg, B.G. Vickrey and F.M. Testa et al., How long does it take for epilepsy to become intractable? A prospective investigation, *Ann Neurol* 60 (2006), pp. 73–9.

in the brivaracetam 100 mg/day ( $p=0.037$ ) group; Therefore, this study did not achieve its primary endpoint of at least 20% reduction over placebo. However, results from the 50 mg group were not statistically significant.

A secondary efficacy endpoint, and primary efficacy endpoint for the European regulatory agencies, was the 50% responder rate, or the proportion of patients experiencing at least 50% reduction in seizure frequency from baseline. The 50% responder rate was 27.3% with brivaracetam 50 mg/day ( $p=0.372$ ) and 36% with brivaracetam 100 mg/day ( $p=0.023$ ), compared to 20.0% for placebo; while the median percent reduction from baseline was 26.83%, compared to 17.03% for placebo.

Pivotal Study 1253 included 392 subjects randomized to receive placebo ( $n=96$ ) or brivaracetam 5 mg/day ( $n=96$ ), 20 mg/day ( $n=99$ ), or 50 mg/day ( $n=101$ ), over a 12-week treatment period. For the primary endpoint analysis, the percent reductions over placebo in the POS frequency per week over the treatment period were -0.9%, 4.1%, and 12.8% in the brivaracetam 5 mg/day ( $p=0.885$ ), 20 mg/day ( $p=0.492$ ), and 50 mg/day ( $p=0.025$ ) groups, respectively. The primary outcome only achieved statistical significance for brivaracetam 50 mg/day vs. placebo ( $p=0.025$ ).

The frequency of concomitant AED use (except levetiracetam) was examined in all three studies, across all brivaracetam dose arms. The clinical reviewer noted the uniformity of AED use across treatment arms. Carbamazepine was the concomitant AED used most frequently in all three trials. One consideration in the analysis of efficacy is the potential synergy of brivaracetam and carbamazepine. The Applicant notes that brivaracetam increased the plasma concentration of carbamazepine epoxide by 37%, 62%, and 98%, at brivaracetam doses of 50 mg/day, 100 mg/day, and 200 mg/day, respectively. However, the clinical pharmacology review team identified a C max increase in carbamazepine epoxide of 164%, and an area under the curve (AUC) increase of 157%. The review team notes that this raises the possibility that concomitant carbamazepine may contribute to brivaracetam efficacy, and may cause biased efficacy outcomes if unequally distributed across treatment arms.

Another consideration in the analysis of efficacy is concomitant use of levetiracetam, which has a mechanism of action that overlaps that of brivaracetam. Studies 1252 and 1253 allowed concomitant levetiracetam use in 20% of patients enrolled. The potential for synergy between these two agents was evaluated. The subset analysis revealed that, in the patient subgroups treated with concomitant levetiracetam, there was a reduced therapeutic effect when compared to those not on concomitant levetiracetam. According to the clinical reviewer, this finding suggests there is no therapeutic synergy between levetiracetam and brivaracetam.

The clinical efficacy reviewer reports that the 50 mg/day dose was not consistent in demonstrating a significant treatment effect, and, therefore, this suggests that 50 mg is the beginning of therapeutic effect. However, the efficacy of brivaracetam is well-supported at the 100 mg/day and 200 mg/day doses.

*Brivaracetam Oral Solution NDA 205838*

Study 1296 was conducted to assess the bioequivalence of the oral solution and commercial tablet. The clinical pharmacology reviewer concludes, “The data support the bioequivalence of the commercial oral solution to the tablets from clinical development.”<sup>6</sup>

#### Brivaracetam Solution for Intravenous (IV) Injection NDA 205837<sup>7</sup>

The proposed indication for brivaracetam solution for intravenous (IV) injection is for use when oral administration is temporarily not feasible. There is expected to be a statement in the Dosing Instructions (Section 2.1) of the Prescribing Information to state that the clinical study experience of IV brivaracetam is limited to four days of consecutive treatment.

Study 1256 compared the bioavailability of the 10 mg IV brivaracetam solution, administered as a 12-second bolus or 15-minute infusion, with the 10 mg oral brivaracetam tablet. The Clinical Pharmacology reviewer concluded that 10 mg of the clinical development oral tablet is bioequivalent to 10 mg of the commercial IV solution, whether administered as a 12-second bolus or a 15-minute infusion.

In a second study, EP0007, a bioavailability/bioequivalence comparison of brivaracetam oral tablets (10 mg, 50 mg, 75 mg, and 100 mg) to brivaracetam IV bolus injection (100 mg) in healthy volunteers was performed. The Clinical Pharmacology reviewer concluded, “The study demonstrates that the commercial solution for injection has comparable bioavailability, in terms of area under the curve (AUC), to the oral tablet used in clinical development. This also held true for lower doses of the clinical tablet (based on dose-normalized AUC values).” In addition, “Brivaracetam can be administered as an IV infusion or IV bolus at the same dose level as oral tablets.”

## **5 Risk Assessment**

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The overall safety population included 3776 subjects from the Applicant’s 53 completed trials, who received at least one dose of brivaracetam. It included Phase 1 volunteers (n=754), adults with epilepsy (n=2531 with POS; n=70 with other seizure types), children with epilepsy (n=173), and subjects with other indications (b) (4) post-herpetic neuralgia, and Unverricht-Lundborg disease; n=248). A total of 1558 patients constituted the safety population in the pooled analysis of Phase 3 placebo-controlled studies in patients with POS, including patients treated with the proposed commercial dose (50 mg/day to 200 mg/day) of brivaracetam (n=1099) and patients treated with placebo (n=459).

For the purpose of this review, an adverse event (AE) was defined as any untoward medical occurrence in a subject temporally associated with the use of brivaracetam, whether or not considered to be related to brivaracetam. Signs or symptoms of seizure disorder were recorded as AEs only if their nature

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<sup>6</sup> Dinsmore, S, Division of Neurology Products, Clinical Efficacy Review of Brivaracetam, dated January 15, 2016.

<sup>7</sup> Ibid.

changed considerably, or if their frequency or intensity increased in a clinically significant manner, compared to the subject's baseline.

### **5.1 SERIOUS ADVERSE EVENTS (SAEs)**

In the pivotal Phase 3 studies, the incidence of SAEs was lower in the total brivaracetam group (2.5%) than the placebo group (2.8%). SAEs of falls and injuries, along with psychiatric disorders, occurred more frequently in brivaracetam-treated subjects than in subjects who received placebo. As with all antiepileptic drugs, brivaracetam should be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

#### ***Psychiatric Adverse Reactions***

According to the clinical safety reviewer, brivaracetam use was associated with suicidality and other psychiatric events, including psychotic events and hostility/aggression, which included rare events of physical assault to family members. The reported incidence of suicidal and self-injurious behaviors in the total brivaracetam group was 1.2%, and included suicide attempt (0.6%) and suicidal ideation (0.6%). A total of 27 patients (1.1%) discontinued treatment because of suicidal and self-injurious behaviors. The Applicant's proposed labeling includes a statement in the Warnings and Precautions section for Suicidal Behavior and Ideation, and has been included for other approved antiepileptic drugs.

### **5.2 ADVERSE EVENTS OF SPECIAL INTEREST (AESIS)**

#### **5.2.1 Hypersensitivity Reactions**

The Applicant provided an analysis of hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DRESS) using actual relevant laboratory data and the vital sign of fever for brivaracetam-treated subjects who discontinued due to treatment emergent adverse events (TEAEs) of pruritus, rash, urticaria, and drug hypersensitivity in the All-Treated Epilepsy Pool, with a categorization of the subjects as definite, probable, or possible DRESS. Following a comprehensive review, while there were brivaracetam-treated subjects with TEAEs coded to DRESS and erythema multiforme, these events were determined by the clinical reviewer to be unlikely related to the treatment drug. (DRESS occurred more than 5 years after brivaracetam use, and erythema multiforme case with negative dechallenge). However, a small percentage of treated subjects (0.2%) experienced hypersensitivity-related SAEs. The risk of hypersensitivity reactions will be included in the Warnings and Precautions section of the prescribing information.

#### **5.2.2 Other Adverse Events of Special Interest**

There were three cases of chronic interstitial nephritis. Two of these cases were determined unlikely to be related to brivaracetam treatment. The clinical reviewer concluded that the third case was unlikely to have been caused by brivaracetam, but it could not be ruled out. The DNP will request postmarketing surveillance and enhanced pharmacovigilance for interstitial nephritis.

### 5.3 DEATHS<sup>8</sup>

A total of 46 fatal cases have been reported in the brivaracetam program as of the safety cutoff of June 25, 2014. No subject died in any of the Phase 1 studies investigating brivaracetam in healthy subjects. In the partial onset seizure (POS) Phase 3 studies, there was a higher percentage of deaths in brivaracetam-treated subjects (0.36%) compared to placebo-treated subjects (0.22%). According to the clinical safety reviewer, the result in the POS controlled studies was mainly driven by 3 deaths due to sudden unexpected death in epilepsy (SUDEP) in brivaracetam-treated patients. Both the Applicant and the clinical reviewer agreed upon the categorization of these 3 deaths as SUDEP. Furthermore, the clinical reviewer calculated the incidence rate of SUDEP in brivaracetam-treated subjects in the POS controlled studies to be 1.8 per 1000 subject-years. This is lower than the rates reported in the literature of 3.5-9.3 per 1000 person-years in subjects with refractory epilepsy.

The incidence rate of SUDEP reported in the brivaracetam program is 7.4 per 1000 person-years, which falls within the reference rate in patients with refractory epilepsy. The clinical reviewer adds, "The rate in the brivaracetam-treated patients in the long term follow-up studies was lower than these historical rates. Therefore, brivaracetam is unlikely associated with an increased risk for SUDEP." The overall mortality rate in the brivaracetam clinical program is 6.1 per 1000 person-years (95% CI 4.3, 8.4), which is comparable to other epilepsy drug development programs and community-based epidemiological studies.

### 5.4 INTRAVENOUS (IV) FORMULATION

The safety of the intravenous (IV) formulation of brivaracetam was demonstrated in a relatively small group of patients (n=177) exposed to the drug briefly in doses of 10 mg to 150 mg, in four clinical trials (0007, 1256A, 1256B, and 1258). The common TEAEs in the IV pool were similar to those of the brivaracetam pivotal trials, which studied the oral tablet formulation. Subjects reported the following AEs related to the route of administration: infusion site pain (2.8%, n=5), injection site extravasation (1.7%, n=3), catheter site inflammation (1.1 %, n=2), injection site erythema (1.1%, n=2), injection site pain (1.1%, n=2), vessel puncture site hematoma (1.1%, n=2), catheter site hematoma, infusion site extravasation, injection site hematoma, injection site inflammation, and injection site irritation (0.6%, n=1 each). However, none of the IV trials included placebo during the treatment periods that would allow for direct adverse event risk comparisons. Without placebo comparator data, the clinical reviewer states it is not possible to understand the role of brivaracetam in these events.

There were no trials designed to compare specific safety endpoints when brivaracetam is administered by bolus vs. infusion. The brivaracetam IV studies did include separate arms that administered the drug as either a bolus (range from over 12 seconds to over 3 minutes) or an infusion (over 15 minutes). There did not appear to be obvious differences when comparing bolus to infusion, although the ability to detect potentially important differences is expected to be limited. The longest duration of exposure to

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<sup>8</sup> Doi M. Division of Neurology Products, Clinical Safety Review for brivaracetam, dated November 5, 2015.

the IV formulation was 4.5 days.<sup>9</sup> The labeling will communicate that the clinical study experience with the IV formulation was limited to four consecutive days of treatment.

## **6 Expected Postmarket Use**

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Brivaracetam and levetiracetam, as well as other AEDs, have similar risks. The likely prescribers for brivaracetam will be neurologists, which are the same prescribers who prescribe levetiracetam and other AEDs. Brivaracetam will be prescribed primarily in an outpatient setting. A medication guide (MG) is included in the Applicant's proposed labeling. The clinical review team will request post-marketing surveillance and enhanced pharmacovigilance for interstitial nephritis.

## **7 Discussion of Need for a REMS**

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The pivotal trials had a greater than 90% retention rate<sup>10</sup> and no major safety signals were identified in the safety review. The safety of brivaracetam for partial onset seizures was established from a database that included 3,776 patients, and is similar to what is reported for other treatments for POS, including levetiracetam. The most important safety concerns of neurological, psychiatric, hypersensitivity events, as well as withdrawal seizures, will be included in the Warnings and Precautions section of the prescribing information. The risks for brivaracetam will be communicated through labeling, including a Medication Guide to communicate important safety information to patients and their caregivers. DRISK and DNP concurred that a REMS is not necessary to ensure the benefits outweigh the risks.

## **8 Risk Management Activities Proposed by the Applicant**

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The Applicant did not submit a REMS with this application, but did submit a proposed risk management plan for brivaracetam, which includes routine pharmacovigilance, a pregnancy registry, and recommendations for labeling. The Applicant states that the proposed labeling and routine reporting/pharmacovigilance are sufficient to mitigate the risks and preserve the benefits of brivaracetam as adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy. They also propose a Medication Guide in the labeling, to educate patients and caregivers.

## **9 Conclusion & Recommendations**

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<sup>9</sup> Boehm G. Division of Neurology Products, Draft of Clinical Safety Review for brivaracetam intravenous formulation, dated November 16, 2015.

<sup>10</sup> Doi M. Division of Neurology Products, Clinical Safety Review for brivaracetam, dated November 5, 2015.

At this time, risk mitigation measures beyond professional labeling are not warranted for brivaracetam for the treatment of partial onset seizures in patients 16 years of age and older with epilepsy. Brivaracetam was effective in reducing the frequency of seizures in the trials. Based on the known safety profile for the drug class and the risks associated with brivaracetam from the clinical trials, a REMS is not necessary to ensure the benefits outweigh the risks for brivaracetam. If new safety information becomes available, please consult DRISK.

## 10 Appendices

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### 10.1 REFERENCES

- UCB. Clinical Overview for Brivaracetam, received November 24, 2014.
- UCB. Brivaracetam U.S. Risk Management Plan, received November 24, 2014.
- UCB. Brivaracetam Partial Onset Seizure Summary of Clinical Efficacy, received November 24, 2014.
- UCB. Summary of Clinical Safety for Brivaracetam, received November 24, 2014.
- Dinsmore S. Division of Neurology Products, Clinical Efficacy Review of Brivaracetam, dated January 15, 2016.
- Doi M. Division of Neurology Products, Clinical Safety Review for brivaracetam, dated November 5, 2015.
- Boehm G. Division of Neurology Products, Draft of Clinical Safety Review for brivaracetam intravenous formulation, viewed November 16, , 2015.
- Bewernitz M and Yang X. Clinical Pharmacology Review of Brivaracetam, dated August 31, 2015.

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/s/  
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02/22/2016

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