# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205836Orig1s000
# 205837Orig1s000
# 205838Orig1s000

# OFFICE DIRECTOR MEMO

**Office of Drug Evaluation-I: Decisional Memo**

| | |
|---|---|
| **Date** | February 18, 2016 |
| **From** | Ellis F. Unger, MD, Director<br>Office of Drug Evaluation 1, Office of New Drugs, CDER |
| **New Drug Application (NDA)#** | 205836 (oral tablets), 205827 (for injection), 205838 (oral solution) |
| **Applicant Name** | UCB, Inc. |
| **Date of Submission** | November 20, 2014 |
| **PDUFA Goal Date (post-3-month extension)** | February 20, 2016 |
| **Proprietary Name / Established (USAN) Name** | Briviact<br>Brivaracetam |
| **Dosage Forms / Strength** | Tablets, oral: 10, 25, 50, 75 and 100 mg; Oral Solution: 10 mg/mL; Injection: 50 mg/5mL |
| **Indication(s)** | …adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy |
| **Action:** | approval |

| **Material Reviewed/Consulted** | **Names of discipline reviewers** |
|---|---|
| Clinical | Steven Dinsmore, Mary Doi, Sally Yasuda, Gerald Boehm |
| Biostatistics | Sharon Yan, Kun Jin |
| Pharmacology/Toxicology | J. Edward Fisher, Lois M. Freed |
| ONDQA Biopharmaceutics | Okpo Eradiri, Angelica Dorantes |
| Clinical Pharmacology/ Biopharmaceutics | Michael Bewernitz, Xinning Yang, Angela Men |
| Bioequivalence Evaluation Inspection | Shila Nkah, Hasan Irier, Xiaohan Cai, Sam H. Haidar |
| Product Quality/Chemistry Manufacturing and Controls (CMC) | Martha Heimann (ATL), Andrei Ponta, Wendy Wilson-Lee, Charles Jewell, Kasturi Srinivasachar, Okpo Eradiri, Angelica Dorantes, Bogdan Kurtyka, Sharmista Chatterjee, Edwin Jao, Lane Christensen, Denise Miller, Neal Sweeney, Ebern Dobbin, Mahesh Ramanadham, Christina Daniel, Dahlia Woody |
| Carcinogenicity (Statistical) | Mohammad Atiar Rahman, Karl Lin |
| Office of Prescription Drug Promotion | Dhara Shah, Mathilda Fienkeng |
| Division of Scientific Investigations | Antoine El Hage, Susan Thompson |
| Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology | Justine Harris, Danielle Harris, Irene Z. Chan |
| Patient Labeling Review | Nyedra Booker, LaShawn Griffiths, Mathilda Fienkeng, Shawna Hutchins, Marcia Williams |
| Controlled Substance Staff | Martin Rusinowitz, Silvia Calderon,<br>Wei Liu (statistics) |
| Associate Director for Labeling | Tracy Peters (acting) |
| Cross-Discipline Team Leader | Norman Hershkowitz |
| Director, Division of Neurology Products | Billy Dunn |
| Division of Pediatric and Maternal Health | Hari C. Sachs, Lynne P. Yao |
| Regulatory Project Manager | Cathleen Michaloski |

# 1. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

The applicant provided substantial evidence of brivaracetam's efficacy for the adjunctive treatment (i.e., with concomitant antiepileptic drug therapy) of partial onset seizures in patients with epilepsy, 16 years and older. The evidence included 3 conventionally-designed, multinational, randomized, double-blind, placebo-controlled trials. The 1° endpoint was seizure frequency.

One study (N01253) was positive at the highest dose studied (25 mg BID), and a second study (N01358) was positive for both doses evaluated (50 and 100 mg BID), although there was no dose-response. A third study, N01252, tested doses of 10 mg BID, 25 mg BID, and 50 mg BID against placebo. The 50 mg BID group was nominally superior to placebo; however, the prospectively planned analysis controlled type-I error thorough a sequential testing procedure that examined the 25-mg dose prior to the 50-mg dose. The results for the lower dose were not statistically significant, rendering the results with the 50-mg dose uninterpretable.

On the whole, the effects on seizure frequency were robust to exploration and consistent across disease-specific subsets and various demographic groups – with one exception. Too few Blacks were included to provide a reliable estimate of efficacy in that population. There is no reason to believe, however, that efficacy would differ in Blacks, based on pharmacokinetic considerations or the drug's mechanism of action.

Brivaracetam's absolute treatment effect was fairly consistent across studies and moderate in magnitude: a mean reduction in the frequency of seizures of ~2 per month, an effect similar to that of other AEDs. An alternative way to consider brivaracetam's benefit is through a responder analysis. Based on a 2° endpoint that defined a "response" as a 50% reduction in seizure frequency over 12 weeks, use of brivaracetam increased the mean number of responders by ~16% (absolute; relative to placebo). On average, therefore, ~1 in 6 treated patients will have a response (50% reduction) through 12 weeks.

The safety of brivaracetam was established from a database of 3,776 subjects, including 1,967 patients with partial onset seizures exposed for $\geq$ 6 months and 1,517 exposed for $\geq$ 12 months. Neurologic and psychiatric adverse reactions appear clearly drug-related:

- Psychiatric disorders include irritability, agitation, depression, anxiety, aggression, and rarely psychosis.
- Neurologic disorders include somnolence, sedation, dizziness, fatigue, malaise, hypersomnia, and lethargy, as well as disturbances in gait and coordination.

In total, over a treatment period of ~12 weeks, some 41% of brivaracetam-treatment patients (at approved doses of 50, 100, or 200 mg daily) reported a psychiatric or neurologic adverse event, compared to 27% in the placebo group. Therefore, the attributable harm to brivaracetam is an excess of ~14% of patients with psychiatric or neurologic adverse reactions.

Other toxicities, although very serious and potentially irreversible (hypersensitivity, suicidality, suicide), are rare.

To the extent that one can compare drugs across development programs, brivaracetam's safety profile seems similar to other anticonvulsants approved for this indication.

The dose-response profile was a relatively flat for both efficacy and adverse reactions.

One case of chronic interstitial nephritis was documented in the long-term uncontrolled experience; causality of brivaracetam could not be assessed. The applicant will be requested to provide postmarketing surveillance and enhanced pharmacovigilance for interstitial nephritis.

Weighing Benefit and Harm:

There are two ways to weigh benefit and harm. As explained above, over a 12-week treatment period, brivaracetam reduced seizures by (mean) ~2 per month. And during those 12 weeks, there was a 14% excess likelihood of experiencing a psychiatric or neurologic adverse reaction, some of which were only mild or moderate in severity.

Alternatively, using the responder analysis described above, the number needed to treat is 6, i.e., 6 patients need to be treated in order to achieve a response in 1. (Note that a response was arbitrarily defined as a 50% reduction in seizure frequency over 12 weeks; alternate definitions would change the number needed to treat). Considering that the excess frequency of adverse reactions is ~14%, the number needed to harm is 7. Of note, however, both numbers are approximations, and we can consider them to be essentially equivalent ($6 \approx 7$). That is, for every patient who achieves a 50% reduction in seizure frequency, 1 patient can be expected to experience a psychiatric or neurological adverse event.

Given equal weighting, therefore, the drug's positive and negative effects seem neutral! But the harms caused by this drug mostly are only mild to moderate in severity. In contrast, seizures are clearly medically important, and a reduction in seizure frequency represents an important benefit. Perhaps most importantly, the harms of the drug appear to be reversible in nature. Without specific monitoring, individual patients should be able to tell if they are having difficulty tolerating the drug; such patients can simply reduce the dose of the drug or discontinue it. Patients who experience sizable reductions in seizure frequency should be able to detect the drug effect and can weigh this benefit against whatever side effects they experience, if applicable. Conversely, patients who obtain relatively small reductions in seizure frequency may not know whether the drug is helping them. Maintenance of a seizure diary could be helpful, so that these patients could also consider their benefits against their side effects.

Levetiracetam is a related drug, widely used for the same indication. We have no data on whether patients who fail levetiracetam could derive benefit from brivaracetam; conversely, we have no data on whether levetiracetam would help patients who fail brivaracetam. The studies do show, fairly convincingly, that brivaracetam has no treatment effect when used on top of concomitant levetiracetam.

Overall, I agree with the Division that the benefit-risk is positive for the drug, and I agree with approval with the agreed upon labeling. Improvement in seizure control is a major medical benefit. The importance and frequency of the harms should not be minimized, but they should be readily detectable without specific monitoring, and with few very rare exceptions, they are not permanent.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Epilepsy is a serious condition. The disease interferes with life style, and can have significant morbidity and mortality. | New treatments are required. |
| **Current Treatment Options** | • Over 18 drugs are used for the treatment of partial onset seizures. Despite the availability of these therapies, however, ~35% of patients with partial onset seizures cannot achieve complete seizure control. | There is clearly a need for new treatments. |
| **Benefit** | • Brivaracetam demonstrated a modest benefit as adjunctive treatment in patients who were, to some extent, resistant to treatment. The mean reduction in seizures from baseline over placebo was 17% to 25% for the highest doses, a reduction of ~2 seizures a month. Based on a responder analysis, ~16% of patients can expect a ≥ 50% reduction in seizure frequency. | The effect size is similar to that of the approved anticonvulsants, and although it may seem marginal in magnitude, the population is refractory to treatment, and these represent mean values. Some patients will receive even greater benefit. |
| **Harm** | • Major side effects are psychiatric and neurologic in nature. They include: depression, anxiety, irritability, agitation, aggression, belligerence, anger, psychosis (rarely), somnolence, fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy, as well as disturbances in gait and coordination. *Importantly, risks that could cause unexpected and irreversible harm are extremely rare (i.e., suicide, hypersensitivity reactions).*<br><br>There was one case of interstitial nephritis; causality of brivaracetam was unknown. | Through 12 weeks, there is a 20% (absolute) increase in the likelihood of experiencing a psychiatric or neurologic adverse reaction, many of which are only mild or moderate in severity. The rates of these adverse reactions are expected to decrease with time. |
| **Risk Management** | • Other than request for limited postmarketing pharmacovigilance regarding interstitial nephritis, there is no need for any other risk management. Patients should be able to detect untoward adverse drug reactions on their own, and the effects seem reversible. | There will be a postmarketing surveillance/enhanced pharmacovigilance for chronic interstitial nephritis. There will be no REMS. |

## 2. Background

Brivaracetam is a new molecular entity (NME), a 2-pyrrolidone derivative, with a proposed indication for the adjunctive treatment of partial onset seizures in patients 16 years and older.

Brivaracetam is chemically and pharmacologically similar to levetiracetam, a drug that has a wide spectrum of anticonvulsant activity, one of which includes the treatment of partial onset seizures. Both are members of the racetam class of drugs. The applicant has submitted 3 international, double-blind, placebo-controlled trials in support of efficacy. The applicant is also requesting approvals for an intravenous formulation and an oral solution formulation based upon a number of bioavailability/bioequivalence and safety studies.

At least 18 other drugs are approved for the treatment of partial onset seizures. Epilepsy affects ~1% of the US population, and the majority of these individuals have partial onset seizures. Approximately 35% of such patients cannot achieve complete seizure control with the presently available drug therapies, underscoring the need for new treatments.

Approvals of most drugs for partial onset seizures have been based on a conventional endpoint of seizure frequency.

## 3. Product Quality

There are 3 formulations of this product. These include tablets: 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg; IV solution: 50 mg/5 mL single-use vial; and oral solution: 10 mg/mL.

All manufacturing facilities are considered acceptable, and the Office of Pharmaceutical Quality recommends approval of the NDA. See other reviews for details.

## 4. Nonclinical Pharmacology/Toxicology

Data reviewed included long-term oral toxicology studies in dogs, rats, and primates; cardiovascular studies; continuous IV infusion studies in rats and dogs; carcinogenicity studies; reproductive and developmental toxicology studies; as well as juvenile animal toxicology studies in rats and dogs.

The nonclinical data were deemed adequate to support marketing approval with appropriate labeling, to include information on embryofetal toxicity, effects on growth and development observed in juvenile studies, and findings in carcinogenicity studies.

## 5. Clinical Pharmacology

Brivaracetam is highly permeable and almost completely absorbed after oral administration. Pharmacokinetics is dose-proportional. The $T_{max}$ is ~1 hour without food. The drug is <20% protein-bound and is metabolized primarily by hydrolysis of the amide group by both hepatic and extra-hepatic amidases. The hydroxylation pathway is primarily mediated by CYP2C19. Metabolites are inactive. The plasma half-life is 7 to 9 hours. Steady state is achieved after 4 to 5 days.

Exposure ($AUC_{0-\infty}$) is little changed in renal failure, and no dose adjustment is required. (The concentrations of some of brivaracetam's metabolites are increased, but they are inactive, and their safety was covered in non-clinical studies.)

Brivaracetam's $AUC_{0-\infty}$ was ~58% higher in patients with Child-Pugh grades A, B, and C compared to healthy controls. Having considered a number of factors with respect to this patient population, the label will recommend dose-reduction for the following reasons: 1) there is little experience with brivaracetam doses > 100 mg BID, doses that would provide the level of exposure that patients with hepatic impairment would experience; 2) monitoring for adverse events in the hepatic impairment study (N0111) was limited to 6 healthy volunteers and 20 patients with varying degrees of hepatic impairment over a relatively short (4-week) period of time; 3) typically, for other anticonvulsants, increases in exposure of this magnitude would require dose adjustment. Thus, for all stages of hepatic impairment, the recommended starting dosage will be 25 mg BID, with a recommended maximum dosage of 75 mg BID.

No significant changes in pharmacokinetics were identified based upon age, sex, race, or ethnicity.

The clinical pharmacology review noted that brivaracetam does not significantly inhibit or induce CYP enzymes. The drug is not a substrate of major transporters, and does not inhibit major transporters.

Potential interactions between brivaracetam (25 mg to 100 mg BID) and other AEDs were investigated in a pooled analysis of plasma drug concentrations in phase 2 and 3 studies. None of the interactions require changes in the dose of brivaracetam. Interactions with carbamazepine and phenytoin can be clinically important, and these effects and specific advice will be provided in labeling.

Meal-related changes in pharmacokinetics were not considered significant; brivaracetam can be administered without regard to meals.

The clinical pharmacology review concluded that with regard to the tablet formulation, the NDA can be approved.

Oral solution

The applicant conducted a study to support bioequivalence of the oral solution and the commercial tablet, and the clinical pharmacology review agreed that single doses of 50 mg brivaracetam tablets and 50 mg oral solution are bioequivalent in terms of $C_{max}$, $AUC_{0-t}$, and AUC, and that these results can be extrapolated to the 100-mg tablets and 100-mg oral solution.

IV formulation

The applicant conducted two studies examining bioavailability/bioequivalence of the IV formulation to the oral tablets.

The first (study N01256) compared the bioavailability of 10 mg of the IV solution (administered as a 12-second bolus or a 15-minute infusion) with a 10-mg oral tablet. The review concluded that the study supports bioequivalence, irrespective of the rapidity of injection.

A second study (EP0007) compared the bioavailability/bioequivalence of the oral tablets (10, 50, 75, and 100 mg) and 100 mg of the IV solution as a 2-minute injection. Bioequivalence with the oral drug was established for the 15-minute IV infusion. The IV bolus formulation was bioequivalent to the oral formulation by AUC; however, $C_{max}$ was 30 to 40% greater with IV bolus injection than oral administration. Dr. Hershkowitz noted that the higher $C_{max}$ is not worrisome, given that the drug was generally well tolerated and IV administration will be performed in inpatient settings. I agree with his conclusions.

An additional intravenous study (N01258), principally intended as a safety study, provided supportive pharmacokinetics data in 105 adults with epilepsy. The clinical pharmacology team concluded that the study was supportive of IV bolus or IV infusion of 100 mg bid brivaracetam.

The safety of IV administration will be discussed in the Section 8 of this memo.

# 6. Clinical Microbiology

No microbiological issues were identified for any of the 3 formulations of the product.

# 7. Clinical/Statistical-Efficacy

Three international, double-blind, placebo-controlled trials provide the evidence of efficacy for brivaracetam. Their features are summarized below:

| Study # | n | Levetiracetam | | Study design | Age range | Patients/group | Treatment period | $1^0$ Efficacy variable |
|---|---|---|---|---|---|---|---|---|
| | | Yes | No | | | | | |
| N01252 | 398 | 76 | 322 | multinational, randomized, double-blind, placebo-controlled, parallel-group | ≥16 to 70 | placebo = 100<br>20 mg/d = 99<br>50 mg/d = 99<br>100 mg/d = 100 | 12 weeks | partial onset seizure frequency per 7 days |
| N01253 | 396 | 76 | 320 | multinational, randomized, double-blind, placebo-controlled, parallel-group | ≥16 to 70 | placebo = 98<br>20 mg/d = 100<br>50 mg/d = 101 | 12 weeks | partial onset seizure frequency per 7 days |
| N01358 | 764 | concomitant levetiracetam excluded | | multinational, randomized, double-blind, placebo-controlled, parallel-group | ≥16 to 80 | placebo = 261<br>100 mg/d = 253<br>200 mg/d = 250 | 12 weeks | partial onset seizure frequency per 28 days |

All studies were similarly designed, parallel, fixed-dose, randomized, double-blind, placebo-controlled studies of patients with refractory partial onset seizures, with or without secondary generalization. All trials included an 8-week baseline period followed by a 12-week treatment period. Various doses of brivaracetam, 10 to 100 mg BID, were compared to placebo. Patients had to be ≥ 16 years old with ≥ 2 partial seizures (with or without generalization) during the preceding 3 months despite use of 1 to 2 AEDs. Dosages of concomitant AEDS had to be stable for ≥ 1 month (3 months for phenobarbital or primidone) prior to treatment. Patients with seizures occurring only in clusters and patients with status epilepticus within 1 year were excluded. Patients had to have ≥ 8 partial onset seizures, whether or not secondarily generalized, during an 8-week baseline period. Concomitant use of levetiracetam, which is structurally similar to brivaracetam, was limited to ~20% of patients in studies N01252 and N01253 and prohibited in study N01358.

There was equal randomization to treatment groups, stratified by geographical region and concomitant levetiracetam use. There was no titration period; i.e., patients were started on their randomized dose. During the treatment period, the study drug dose could be reduced once for tolerability reasons. Following the treatment period, subjects could enter a long-term open-label study or be down-titrated over 1 to 4 weeks.

Each patient was to record their seizures on a daily record card, documenting the date, number, and type of seizures. The 1° endpoint was the frequency of partial onset seizures (Type I seizures) during the treatment period. Seizure frequencies were expressed per 7 days in studies N01252 and N01253 and per 28 days in study N01358. Missing data were imputed using last observation carried forward. Days with missing data were not included.

Seizure frequencies were log-transformed to normalize the distribution, and analyzed using an ANCOVA model, including treatment and stratification effects as factors and the log-transformed baseline seizure frequency as a covariate.

The primary analyses, though referred to as “intent-to-treat,” were really modified intent-to-treat because they excluded patients who had not received a dose of the test drug, as well as patients without outcome data. One study also excluded 3 randomized subjects because of concerns with respect to protocol noncompliance and/or lack of adherence to good clinical practice guidelines. (The small numbers of patients excluded from the modified intent-to-treat analyses have no consequence on the overall results.)

Secondary endpoints assessed seizure frequency in various ways, and additional 2° endpoints assessed various patient-reported outcomes.

Each active treatment group was compared to placebo. Type-I error was controlled as follows:

- Study N01252: sequential testing procedure ($\alpha$ = 0.05): 50 mg/day, then 100 mg/day, then 20 mg/day. It is not clear that the applicant conferred with the Division; *it seems obvious that the highest dose should have been examined first*.
- Study N01253: sequential testing procedure ($\alpha$ = 0.05): 50 mg/day, then 20 mg/day, then 5 mg/day.
- Study 01358: The Hochberg procedure was used ($p < 0.05$; with alternate of $p < 0.025$ if the largest $p$-value is > 0.05).

Results:

Study N01252 was conducted in Eastern Europe, Western Europe, and India, and included no patients from North America and no Blacks. Study N01253 was conducted in Latin America, North America, and Australia. Study N01358 was conducted in Eastern and Western Europe, North America, Asia/Pacific, and Latin America.

Demographic variables were reasonably well matched among the arms of the studies. Most patients were Caucasian (74%) or Asian (13%). Blacks were largely underrepresented in the development program, accounting for only 2.5% of patients in the 3 efficacy trials (only 27 Blacks were exposed to brivaracetam in the 3 efficacy studies).

Patient retention was acceptable in the 3 studies, ranging from 89% to 95% in the brivaracetam groups with similar retention rates in the placebo arms. Adverse events accounted for 4 to 8% of discontinuations across all treatment arms. There were few missing data; missing data were generally limited to patients who discontinued prematurely.

Baseline disease characteristics and therapies were consistent among the treatment groups of each study. Median duration of epilepsy and baseline seizure frequencies were similar in the 3 studies and similar among the treatment groups. Patients were typically taking 2 AEDs (70 to 83%) at entry.

Subgroup analyses for gender, age and geographic region performed by Dr. Yan were complicated by the skewed distribution of seizure frequency and the limited sizes of the subgroups. Nevertheless, to the extent the analyses could be interpreted, substantial discrepancies in treatment effect were not apparent.

As noted in the Addendum to Statistical Review and Evaluation, an error in the applicant's calculation of percent reduction of seizure frequency was identified late in the review. The percent reductions in seizure frequency were originally underestimated, affecting the 7-day seizure frequency more than the 28-day seizure frequency. The values are reported below are corrected.

**Analysis by Study**

*Study N01252*

A total of 227 males (57%) and 171 females (43%) enrolled in this study. Mean age was 37 years. The majority of subjects were Caucasian (77%). The remaining subjects were of Asian descent. The table presents the analysis of the primary endpoint of study N01252. As noted above, the sequential testing procedure evaluated the comparison of the 50-mg dose group vs. the placebo group first, and the difference was not statistically significant. Thus, formal hypothesis testing stopped at that point; analysis of the 100-mg dose group vs. placebo can only be considered exploratory in nature. There was some sympathy on the review team for displaying the *p*-value for the comparison of the 100 mg/d group vs. placebo (which was nominally statistically significant), but this would violate the principal of restricting analyses to those prospectively planned.

**Study N01252 – Results of 1° endpoint: seizure frequency per week**

| | Placebo | Brivaracetam | | |
|---|---|---|---|---|
| | N=100 | 20 mg/day N=99 | 50 mg/day N=99 | 100 mg/day N=100 |
| Median seizure frequency per 7 days – at baseline | 2.07 | 1.93 | 1.80 | 2.02 |
| Median seizure frequency per 7 days - on treatment | 1.75 | 1.34 | 1.49 | 1.26 |
| Adjusted mean % reduction in seizure frequency vs. placebo | | 9.9 | 9.5 | 17.0 |
| *p*-value | | - | NS | - |

According to Dr. Yan's analyses, the nominal treatment effect in the 100-mg group was consistent across subsets by sex, age, and race (Caucasian vs. 'other').

Dr. Dinsmore notes that the analysis of the 2° endpoint QOLIE-31-P demonstrated no difference between brivaracetam and placebo.

*Study N01253*

A total of 195 males (49%) and 201 females (51%) were enrolled in this study. Mean age was 38 years. The majority of subjects were Caucasian (72%); 4% were Black. The table shows the analysis of the primary endpoint. Only the 50-mg/day dose was statistically significantly different from placebo. Marked deviation from the normality assumption was evident, but sensitivity analyses using a linear mixed-effects model and a rank-ANCOVA model on the untransformed data confirmed the results of the 1° analysis.

In the 50 mg/day treatment arm, there was a (mean) 17% reduction in seizure frequency over placebo, which corresponds to a mean reduction of ~1.8 seizures per 28 days.

**Study N01253 – Results of 1° endpoint: seizure frequency per week**

| | Placebo | Brivaracetam | | |
|---|---|---|---|---|
| | N=96 | 5 mg/day N=96 | 20 mg/day N=99 | 50 mg/day N=101 |
| Median seizure frequency per 7 days – at baseline | 2.63 | 2.32 | 2.23 | 2.85 |
| Median seizure frequency per 7 days - on treatment | 2.15 | 1.80 | 1.96 | 1.70 |
| Adjusted mean % reduction in seizure frequency vs. placebo | | -1.2 | 5.4 | 16.9 |
| *p*-value | | - | NS | 0.025 |

Per Dr. Yan's analyses, the treatment effect in the 50-mg group was relatively consistent across subsets of sex, age, race (Caucasian vs. 'other'), and geographic location.

A 2° endpoint of responder status ("responder" ≡ ≥ 50% reduction in partial onset seizure frequency over the treatment period; "non-responder" ≡ < 50% reduction) provided an odds

ratio of 2.51 (95% confidence interval: 1.27 to 4.96). The actual responder rates were 16.7% in the placebo group vs. 32.7% in the brivaracetam 50 mg/d group (see Clinical Review by Dr. Dinsmore, page 84). Thus, on average, ~16% of patients could expect a 50% reduction in seizure frequency over 12 weeks.

As noted by Dr. Dinsmore, no treatment effect was noted for the QOLIE-31-P.

*Study N01358*

This was the largest study, with 760 subjects enrolled. The proportions of males (48%) and females (52%) enrolled were similar. Mean age was 39.5 years. The majority of subjects were Caucasian (72.4%); 3.4% were Black. Approximately half the patients were enrolled from the EU region, and ~25% were enrolled from North America. The table shows the analysis of the 1° endpoint.

The results were statistically significant for both the 100 mg/d and 200 mg/d doses. Despite a 2-fold difference in dose, the reduction in seizures was ~25% for both treatment groups, which would correspond to a mean reduction of 2.4 seizures per 28 days in both brivaracetam treatment groups.

**Study N01358 – Results of 1° endpoint: seizure frequency per 28 days**

| | **Placebo** | **Brivaracetam** | |
|---|---|---|---|
| | **N=259** | **100 mg/day N=252** | **200 mg/day N=249** |
| Median seizure frequency per 7 days – at baseline | 10.0 | 9.5 | 9.3 |
| Median seizure frequency per 7 days - on treatment | 8.7 | 6.3 | 5.8 |
| Adjusted mean % reduction in seizure frequency vs. placebo | | 25.2 | 25.9 |
| *p*-value | | <0.001 | <0.001 |

According to Dr. Yan's analyses, the treatment effects in both brivaracetam groups were relatively consistent across subsets of sex, age, race (Caucasian, Asian, 'other'), and geographic location.

Persistence of effect; seizure worsening:

Using the methodology of unadjusted median percent reduction in seizure frequency and an ANCOVA model with 4-, 8-, and 12-week epochs, Dr. Dinsmore found no evidence of loss of treatment effect of brivaracetam. He also assessed seizure-related adverse events, and found no evidence of seizure worsening with brivaracetam.

A 2° endpoint of responder status ("responder" ≡ ≥ 50% reduction in partial onset seizure frequency over the treatment period; "non-responder" ≡ < 50% reduction) provided odds ratios of 2.19 and 2.39 for the two treatment groups (both were statistically significant), corresponding to responder rates of ~22% in the placebo group vs. ~38% in the two brivaracetam treatment groups (see Clinical Review by Dr. Dinsmore, page 84). Thus brivaracetam's mean absolute treatment effect was 16%, i.e., 16% of patients could expect a 50% reduction in seizure frequency over 12 weeks.

Use of levetiracetam:

Brivaracetam is structurally similar to levetiracetam; therefore, a number of questions arise with respect to concomitant use of the two drugs. The first question is whether use of the two drugs is additive. For patients whose seizures are not adequately controlled on levetiracetam, would the addition of brivaracetam in improve seizure control? Conversely, for patients whose seizures are not adequately controlled on brivaracetam, would addition of levetiracetam improve seizure control? And for patients whose seizures were not well controlled with levetiracetam, what is the likelihood that brivaracetam (alone) would be effective?

One-fifth of patients in studies N01252 and N01253 were taking concomitant levetiracetam; these studies evaluated (collectively) 5-, 20-, 50-, and 100-mg daily doses of brivaracetam. Drs. Yan and Dinsmore found no additional reduction in seizure frequency in the subset of patients who were on concomitant levetiracetam. Dr. Dinsmore's analysis (shown below, adapted from the Clinical Review, page 140, Table 57) evaluates the combined data from studies N01252 and N01253. For each brivaracetam dose group, the median frequency of seizures tended to be higher when levetiracetam was used as a concomitant medication. The interpretation of this non-randomized analysis is not straightforward (patients were not randomized to levetiracetam [Y/N]), but the data in no way suggest that addition of brivaracetam to levetiracetam further lowers the frequency of seizures. With respect to patients previously on levetiracetam, the data are not helpful.

Studies N01252 and N01253: median on-treatment seizure frequency by treatment arm, with and without concomitant levetiracetam (n=790)

| Treatment Group | Levetiracetam ? | Patients (N) | Median Treatment Seizure Frequency |
|---|---|---|---|
| Placebo | yes | 37 | 8.3 |
| Placebo | no | 159 | 7.5 |
| Brivaracetam 5 mg | yes | 18 | 10.7 |
| Brivaracetam 5 mg | no | 78 | 6.9 |
| Brivaracetam 20 mg | yes | 37 | 8.7 |
| Brivaracetam 20 mg | no | 161 | 5.6 |
| Brivaracetam 50 mg | yes | 39 | 9.1 |
| Brivaracetam 50 mg | no | 161 | 5.6 |
| Brivaracetam 100 mg | yes | 20 | 9.8 |
| Brivaracetam 100 mg | no | 80 | 4.5 |

Thus, for patients whose seizures were not well controlled with levetiracetam, the likelihood that brivaracetam would be effective is unknown. Only a study of brivaracetam in levetiracetam non-responders (or inadequate responders) could answer this question.

Dr. Hershkowitz suggests that the conclusions, above, are only applicable to brivaracetam doses of 50 mg/day and 100 mg/day, because there are no data for the 200-mg dose. I would note, however, that if there is no evidence that levetiracetam adds to brivaracetam at doses of 100 mg and below, we should have no reasonable expectation that levetiracetam would add to the effect of brivaracetam at even higher doses.

Use of carbamazepine:

Brivaracetam appears to increase the levels of the active epoxide metabolite of carbamazepine. Drs. Dinsmore and Yan performed analyses to consider whether this interaction influenced the effect size in patients started on brivaracetam who were, and were not, on concomitant carbamazepine. Neither reviewer found an impact on brivaracetam's effect size.

**Efficacy conclusions:**

I concur with the Division that the applicant has presented substantial evidence of efficacy. The applicant submitted two positive multinational, randomized, double-blind, placebo-controlled studies: study N01253 showed a statistically significant treatment effect for the 50 mg/d dose; the much larger study N01358 demonstrated statistically very persuasive effects for the 100 and 200 mg/d doses, with a 25% reduction in seizure frequency. Study N01252 was statistically negative, but nevertheless suggested a treatment effect at 100 mg/d. Brivaracetam's absolute effect size is a ~2 per month reduction in the frequency of seizures, an effect size similar to other AEDs. Results were fairly consistent across subgroups of sex, age, and race. Although only small numbers of Black patients were enrolled in the studies, there is no a priori reason to be concerned that they would respond differently than Caucasians.

In considering the various doses, the Division concluded that the 50-mg daily dose produced a smaller magnitude of effect than the 100-mg dose, and the effect of the 200-mg daily dose was similar to that of 100-mg daily dose. Based on this information, the Division recommends an initial dose of 100 mg daily. And because tolerability of the 200-mg dose is not markedly worse than the 100-mg dose, and given that there is individual variability in drug response, the Division suggests that the label advise a dose increase if seizures are inadequately controlled and the patient is tolerating the drug. Although the overall results for the 100- and 200-mg daily doses were similar, there may be some patients who would derive more benefit from the higher dose. Notably, the toxicity of the drug seems reversible (see Section 8). Finally, the Division recommends that if the 100-mg dose is not tolerated, that a trial of 50 mg daily is worthwhile, based on the results of study N01253.

# 8. Safety

Dr. Doi performed the primary safety review, with secondary and tertiary reviews by Drs. Yasuda and Hershkowitz.

In total, the safety database included data from 3776 subjects exposed to brivaracetam, including 754 subjects in phase 1 studies, 2531 patients with partial onset seizures, and 173 pediatric patients. The remaining patients included those with other seizure disorders and other diagnoses (e.g., essential tremor). A total of 1967 patients with partial onset seizures were exposed for ≥ 6 months with 1517 exposed for ≥ 12 months. The majority of patients received relevant doses, such that the numbers exceed those in the ICH E1 Guideline.

The randomized, double-blind, placebo-controlled phase 3 epilepsy studies provided the primary support of safety, with 1099 patients receiving brivaracetam and 459 receiving placebo. The placebo-controlled portions of these studies were 12 weeks in duration. These data were supplemented by open-label extension studies and other studies.

Safety of intravenous administration will be discussed separately.

Overall, ~23% of patients in the safety database were from North America (21% from the United States and 2% from Canada), 25% and 20% were from Western and Eastern Europe, respectively, 17% were from Latin America, and 14% were from Asia/Pacific countries.

**Deaths**

A total of 44 deaths were reported by the applicant: 35 in the partial onset seizure database and 9 in other indications. In the controlled epilepsy studies, there was 1 death in 686 patients on placebo (0.15%) and 5 deaths in 1717 patients on brivaracetam (0.29%). Three (3) of the deaths in the brivaracetam groups were attributed to sudden unexpected death in epilepsy (SUDEP), deemed most likely to result from the underlying seizure disorder rather than from a drug effect. Moreover, 2 of the 3 patients who succumbed to SUDEP had been off brivaracetam for 9 to 14 days, making the drug unlikely to be a contributing factor. The other 2 deaths were attributed to drowning and respiratory failure after a witnessed seizure. The Division noted that such causes of death are not uncommon in this patient population and are not likely to be drug-related.

Upon further examination of SUDEP cases in the database, the Division calculated a SUDEP rate of 1.8 per 1000 patient-years, which is lower than reported rates in a refractory epilepsy population. Thus, the Division concluded that it is unlikely that brivaracetam increases the risk of SUDEP.

Additional deaths in all partial onset seizure studies (controlled and open-label) included 7 associated with neoplasms, 2 suicides, 2 associated with status epilepticus or seizures, 3 cardiovascular events, 1 fall, and 1 multi-organ failure. Lacking a consistent cause or pattern of deaths, I agree with the Division that it is difficult to implicate a causal role for brivaracetam.

**Serious Adverse Events**

There were only 49 treatment-emergent serious adverse events reported in the controlled portions of the 3 double-blind, placebo-controlled efficacy studies for partial onset seizures. Dr. Doi noted that the incidence of serious adverse events (SAEs) was similar in patients who received brivaracetam and placebo. In Table 49 of her review, Dr. Doi tabulated the serious adverse events for system-organ-classes that included ≥ 2 subjects in the brivaracetam group and greater numbers in the brivaracetam group than in the placebo group.

I examined the ADAE.xpt datafile for treatment-emergent serious adverse events in the 3 phase 3, double-blind, placebo-controlled efficacy studies for partial onset seizures, eliminating adverse events where: PS1FL (pool safety 1 flag) ≠ 1, TRTEMFL (treatment emergent analysis flag) ≠ Y, and AESER (serious event) ≠ Y. Median exposure during the placebo-controlled, double-blind period was ~12 weeks.

Two points are noteworthy. First, there is a trend in favor of excess serious seizure-related adverse events in the placebo group, which supports (weakly) the efficacy of brivaracetam.

Second, as noted by Dr. Doi, brivaracetam appears to cause excess psychiatric serious adverse events. Dr. Doi found 5 such events in the brivaracetam group vs. 0 in placebo. I added amnesia, agitation, and epileptic psychosis to this category, such that I found 8 (0.7%) serious adverse events for the brivaracetam group vs. 0 for placebo. As Dr. Doi points out, the preponderance of psychiatric events is similar to that observed for levetiracetam, a drug with similar chemical structure and presumed mechanism of action.

| | placebo | brivaracetam |
|---|---|---|
| **N** | **459** | **1099** |
| **Cardiovascular, n (%)** | **2 (0.4%)** | **3 (0.3%)** |
| ACUTE MYOCARDIAL INFARCTION | | 1 |
| CORONARY ARTERY STENOSIS | 1 | |
| SYNCOPE | | 1 |
| ANGINA PECTORIS | 1 | |
| CHEST PAIN/DYSPNEA | | 1 |
| **Seizure, n (%)** | **6 (1.3%)** | **6 (0.5%)** |
| CONVULSION | 4 | 2 |
| EPILEPSY | 1 | |
| GRAND MAL CONVULSION | | 1 |
| POSTICTAL STATE | 1 | |
| STATUS EPILEPTICUS | | 2 |
| SEIZURE CLUSTER | | 1 |
| **Injury, n (%)** | **2 (0.4%)** | **7 (0.6%)** |
| CRANIOCEREBRAL INJURY | | 1 |
| FALL | | 3 |
| FRACTURE | 1 | 3 |
| JOINT DISLOCATION | 1 | |

| | placebo | brivaracetam |
|---|---|---|
| **N** | **459** | **1099** |
| **Infection, n (%)** | **2 (0.4%)** | **3 (0.3%)** |
| LOCALISED INFECTION | | 1 |
| PNEUMONIA | | 1 |
| MENINGITIS VIRAL | 1 | |
| PNEUMONIA | 1 | |
| BRONCHITIS | | 1 |
| **Psychiatric, n (%)** | **0 (0%)** | **8 (0.7%)** |
| EPILEPTIC PSYCHOSIS | | 1 |
| ADJUSTMENT DISORDER | | 2 |
| AGITATION | | 1 |
| AMNESIA | | 1 |
| CONVERSION DISORDER | | 1 |
| PSYCHOTIC DISORDER | | 2 |
| **Misc** | | |
| PREGNANCY | 1 | |
| THYMOMA | 1 | |
| GASTRITIS EROSIVE | | 1 |

Dr. Doi noted that even when exposure in the long-term uncontrolled periods of the studies was included, there were no reported serious adverse events of hepatic failure, agranulocytosis, aplastic anemia, drug reaction with eosinophilia and systemic symptoms, pancytopenia, rhabdomyolysis, Stevens Johnson syndrome, toxic epidermal necrolysis, torsade de pointes, ventricular fibrillation, ventricular tachyarrhythmia, or ventricular tachycardia.

### Discontinuations

Dr. Doi noted that in the phase 3, double-blind, placebo-controlled trials, a higher percentage of subjects in the brivaracetam group discontinued secondary to an adverse event (6.6%) than in the placebo group (3.5%). There was no clear dose-response. The difference between groups was largely a result of adverse events in the nervous system and psychiatric disorder classes. Specific preferred terms more frequent in the brivaracetam group than the

placebo group were dizziness, convulsion, headache, depression, aggression, insomnia, irritability, ataxia, agitation, dyspnea, and fall.

**Adverse Events of Special Interest**

*Neurologic*

Adverse events in the neurologic system disorder system-organ-class were commonly observed in the phase 3, double-blind, placebo-controlled studies. Dr. Doi found that such events were reported in some 37% of brivaracetam-treated patients, compared to 29% of placebo patients.

Dr. Doi notes that this was largely driven by somnolence and fatigue. In her analysis, there appeared to be a greater risk for these events the first 7 days of exposure.

The Division has made the decision to include neurological adverse reactions as a warning (Section 5.2) in the label, and to underscore the risks of somnolence/fatigue as well as dizziness/disturbances in gait and coordination. This action is consistent with all of the analyses, and all on the review team agree with this approach.

*Falls*

Dr. Doi analyzed of falls and injury data from the phase 3 studies and found a high incidence for such events, slightly greater in brivaracetam-treated patients than in placebo. Although Dr. Doi recommended that these events be labeled as a warning in Section 5, Dr. Yasuda disagreed, noting that the treatment differences are not large, and they are confounded by seizure occurrence. Dr. Hershkowitz agreed with Dr. Yasuda. My own analysis of falls does not show an excess of such events in the brivaracetam treatment groups, and I agree that they should not be called out as a warning in labeling.

*Psychiatric*

Dr. Doi provided an extensive analysis of adverse events in the psychiatric disorders system-organ-class. She identified such adverse events in ~13% of brivaracetam-treated patients vs. ~8% in placebo. The difference was driven largely by anxiety and depression. As noted above, she noted that psychiatric serious adverse events were more common with brivaracetam than placebo (5 vs. 0), whereas I found 8 vs. 0.

An important issue is whether psychosis or psychotic symptoms should be labeled, as there is a definite comorbidity between epilepsy and psychosis. Dr. Doi reviewed the cases associated with psychotic and/or hostility/aggression and noted that, “While some events developed after a long latency or were confounded by concomitant medications (levetiracetam) or previous history, there were several cases with temporal association with brivaracetam initiation and positive de-challenge without prior history of psychiatric disease.”

Based upon Dr. Doi’s review of the data, Drs. Yasuda and Hershkowitz agree that information on psychiatric adverse reactions should be included in Section 5.3 of the label. They note that brivaracetam is similar to levetiracetam (see above), which has labeling for psychosis and other behavioral effects described above.

*Suicidal behavior and ideation*

Suicidal behavior and ideation are uncommon, but they do occur in patients with seizures taking AEDs. Few are expected (and few were reported) in a safety database of this size. Suicidality will be included as a warning in Section 5.1 of the label as part of this Division's class labeling policy for AEDs.

*Hypersensitivity*

Dr. Doi found a small but greater incidence for adverse events classified with hypersensitivity preferred terms (0 subjects taking brivaracetam < 50 mg/day and 0.2% of subjects taking brivaracetam ≥ 50 mg/day, compared to 0 placebo patients).

Dr. Doi noted that one patient suffered angioedema with close temporal association to initiation of brivaracetam and a positive de-challenge. She also found a case with the development of sudden dyspnea with rhonchi associated myalgia and asthenia, which resolved after treatment with steroids and brivaracetam discontinuation. Thus, Dr. Doi recommended that information about angioedema and anaphylaxis be placed in Section 5.4 of the label as a warning. Drs. Yasuda and Hershkowitz agreed that a description of this case should be included in the label, but because of the absence of documentation of the full syndrome they agreed that the section should be described as "bronchospasm and angioedema."

*Cardiovascular*

The Division was not convinced that there was a signal for cardiovascular adverse events, with the possible exception of bradycardia. They found 3 patients (0.4%) in the brivaracetam ≥ 50 mg/day group, none in the < 50 mg/day group and none in placebo who were reported to have bradycardia. None of these were serious adverse events. I actually found 4 brivaracetam-treated patients with reported bradycardia, vs. none in placebo, but, like the Division, in isolation, I do not find this imbalance suggestive of drug causality.

*Hepatobiliary disorders*

The Division conducted a number of careful analyses, but found no signal for hepatobiliary disorders.

*Infectious Disorders*

The Division conducted a number of careful analyses, but found no signal for infectious disorders.

*Renal Disorders*

Dr. Doi analyzed found no imbalances in her analyses of renal adverse events. In my own analysis of adverse events from the controlled portions of the phase 3 studies, I found only 3 patients for whom renal adverse events were reported (preferred terms were "azotaemia," "renal failure acute," and "creatinine renal clearance abnormal"), and all were in the placebo group.

Dr. Doi identified a serious adverse event of renal failure in a 26 year-old male where the biopsy showed chronic tubulointerstitial nephritis with nephrosclerosis. Brivaracetam was

discontinued without resolution, and there was no other information. Dr. Doi did not believe this could be definitively attributed to brivaracetam, but recommend a postmarketing surveillance/enhanced pharmacovigilance for chronic interstitial nephritis, and the Division agreed.

**Adverse Events for Section 6 of the Label**

Dr. Doi established the following criteria for providing labeling information on 'common' adverse events:

- ≥ 2% in either the 100- or 200-mg dose groups (and > placebo) in the phase 3 placebo-controlled trials or;
- ≥ 2% in the 50-mg dose group only (and > placebo) in the phase 3 placebo-controlled trials and ≥ 2% in either the 100- or 200-mg dose group (and > placebo) in study N01358

To avoid dividing similar preferred terms into more than one grouping, Dr. Doi presented adverse events as follows: visual disorders = vision blurred, diplopia or visual impairment; nausea and vomiting symptoms = nausea or vomiting; memory loss (excludes dementia) = memory impairment or amnesia; paraesthesias and dysaesthesias = paraesthesia or dysaesthesia; cerebellar coordination and balance disturbances = ataxia, balance disorder, coordination abnormal, or nystagmus; anxiety symptoms = anxiety, agitation, or nervousness. Her particular groupings are denoted by the symbol "^".

**Table 93. Adverse drug reactions for labeling, Pool S1***

| MedDRA (Version 15.0) Primary SOC PT^ | PBO (N=459) % | BRV randomized dose/day 50mg (N=200) % | 100mg (N=353) % | 200mg (N=250) % |
|---|---|---|---|---|
| **Ear and labyrinth disorders** | | | | |
| Vertigo | 2 | 2 | 3 | 2 |
| **Eye disorders** | | | | |
| Visual disorders^ | 2 | 4 | 3 | 2 |
| **Gastrointestinal disorders** | | | | |
| Nausea/vomiting symptoms^ | 3 | 8 | 5 | 4 |
| Constipation | <1 | 3 | 1 | 2 |
| Toothache | 1 | 2 | <1 | 2 |
| **Infections and infestations** | | | | |
| Nasopharyngitis | 3 | 3 | 3 | 4 |
| Bacteriuria | 1 | 1 | 1 | 2 |
| Influenza | 1 | 2 | 2 | 1 |
| **Injury, poisoning and procedural complications** | | | | |
| Fall | 1 | 2 | 1 | 1 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 1 | 3 | 1 | 2 |
| Hyponatraemia | <1 | 0 | 1 | 2 |
| **Nervous system disorders#** | | | | |
| Somnolence | 9 | 12 | 16 | 17 |
| Dizziness | 7 | 12 | 9 | 14 |
| Fatigue | 4 | 7 | 8 | 12 |
| Cerebellar coordination and balance disturbances^ | 1 | 4 | 2 | 3 |
| Memory loss (excl dementia)^ | 1 | 3 | 1 | 2 |
| Tremor | 1 | 2 | 1 | 2 |
| Sedation | 0 | 0 | 0 | 2 |
| Paraesthesia/dysaesthesias^ | 1 | 2 | 1 | 1 |
| **Psychiatric disorders** | | | | |
| Anxiety symptoms^ | 2 | 5 | 3 | 3 |
| Irritability | 1 | 5 | 3 | 3 |
| Insomnia | 2 | 5 | 2 | 2 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 2 | 2 | 3 | 2 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Pruritus | 1 | 2 | 1 | 2 |
| Eczema | 0 | 1 | 0 | 2 |
| Rash | 1 | 2 | 1 | 1 |

Based on Dr. Doi's groupings of preferred terms, adverse events that met these criteria include nausea and vomiting, somnolence, dizziness, cerebellar coordination and balance disorders, anxiety, and irritability.

Given that there was not a consistent dose-response (save for somnolence), a more precise estimate of adverse event frequencies can be obtained by combining all of the brivaracetam groups (for the to-be-marketed doses: 50, 100, and 200 mg/day). My analysis, below, highlights in red adverse events that are ≥ 1.5% (absolute) more frequent in brivaracetam than placebo. This basic display will be included in Section 6 of labelling.

| | % brivaracetam | % placebo | risk difference |
|---|---|---|---|
| **Nervous system** | | | |
| somnolence/sedation | 8 | 16 | 7.2 |
| dizziness | 7 | 12 | 4.8 |
| headache | 10 | 10 | -0.7 |
| fatigue | 4 | 9 | 5.0 |
| ataxia, balance, coordination, nystagmus | 1 | 3 | 1.5 |
| memory impairment | 1 | 1 | 0.3 |
| **psychiatric** | | | |
| anxiety, nervousness, agitation | 2 | 3 | 1.5 |
| irritability | 1 | 3 | 2.1 |
| insomnia | 2 | 3 | 1.3 |
| depression | 1 | 2 | 1.2 |
| **ocular** | | | |
| * | 2 | 3 | 1.2 |
| **gastrointesinal** | | | |
| nausea/vomiting | 3 | 5 | 2.6 |
| constipation | 0 | 2 | 1.8 |
| upper abdominal pain | 1 | 2 | 0.7 |
| decreased appetite | 1 | 1 | 0.8 |
| **miscellaneous** | | | |
| back pain | 1 | 1 | 0.6 |
| extermity pain | 1 | 1 | -0.2 |
| myalgia | 1 | 1 | 0.2 |
| eczema | 0 | 1 | 0.6 |

*vision blurred, diplopia, visual impairment, visual acuity reduced

## Laboratory Findings

*Hematology*

Levetiracetam, a drug that is structurally similar to brivaracetam, is known to cause hematologic abnormalities, including decreases in hemoglobin/hematocrit, increases in eosinophil count, and decreases in neutrophil count. Cases of agranulocytosis have been reported during marketing.

Dr. Doi performed extensive analyses of the frequencies of shifts from baseline for hematologic indices, and found consistent but small shifts to lower leukocyte and neutrophil counts for brivaracetam doses ≥ 100 mg/day compared to placebo. The review team considered her findings, and will place this information in Section 6 of labeling (adverse

reactions). Specifically, 1.8% of brivaracetam-treated patients and 1.1% of placebo-treated patients had a reported total leucocyte count < 3 X $10^9$/L; 0.3% of brivaracetam-treated patients and no placebo treated patients had a reported total leucocyte count < 1 X $10^9$/L.

*Chemistry*

The Division concluded that the incidence of clinically significant abnormalities in chemistry parameters was low and generally similar between brivaracetam and placebo.

*Vital Signs*

The Division found no evidence that brivaracetam has meaningful effects on blood pressure or orthostatic blood pressure.

*Electrocardiogram*

The Division found no evidence that brivaracetam causes important changes in ECG parameters. A thorough QT study was negative.

**Intravenous Studies**

The applicant is seeking approval for an intravenous formulation of brivaracetam (ivbrivaracetam). The safety database included of a total of 177 exposures from 3 clinical pharmacology studies in normal subjects who received 1 to 2 doses of the drug through up to 7 days. A single 105-patient double-dummy study was included that compared oral tablets to IV administration, where patients received up to 9 doses over 4.5 days. These data were reviewed by Dr. Boehme.

A number of studies were performed to examine the pharmacokinetics and safety parameters of the IV formulation. The clinical pharmacology review determined that this formulation may be labeled for both a 15-minute infusion and a 2-minute (slow) bolus.

These studies are briefly described as follows:

- N01256-A: a 3-way crossover trial in healthy subjects (n = 24) examining single doses of brivaracetam administered as a 10-mg tablet, 10-mg IV bolus (12-second bolus), and 10-mg IV infusion (over 15 minutes).
- N01256-B: a study in 4 groups of 6 healthy subjects (n = 24) comparing administration of a single dose of ivbrivaracetam at two rates one week apart: 1) 25 mg administered as a 15-minute infusion and a 30-second bolus, 2) 50 mg administered as a 15-minute infusion and a 1-minute bolus, 3) 100 mg administered as a 15-minute infusion and a 2-minute bolus, 4) 150 mg administered as a 15-minute infusion and a 3-minute bolus.
- Study EP0007: a 5-way, crossover, single-dose trial in healthy subjects (n = 25) comparing oral tablets to 2-minute infusions of ivbrivaracetam at dosages of 10, 50, 75, and 100 mg.
- Study N01258: a 4-arm, randomized, parallel-group trial in adult seizure patients (n = 105). Subjects were started on either placebo or 100-mg brivaracetam tablets BID and were treated for 7 days. Each patient was then switched to 100 mg of brivaracetam BID as a 15-minute infusion or a 2-minute bolus.

As Dr. Boehm notes, the studies had the disadvantage of examining relatively small numbers of patients for short periods of time, and there was no placebo comparator. Nevertheless, there was no apparent difference in the numbers or types of adverse events reported with respect to the oral formulation. The most common adverse events observed with ivbrivaracetam were somnolence, fatigue, dizziness, and headache. None of these were serious adverse events.

Typical injection-related adverse events were reported in 5-10% of patients. None were serious and none led to discontinuation.

Dr. Boehm found no apparent differences between infusion and 2-minute bolus injection, although there was apparently a slight increase in blood pressure in patients who received an infusion (but not a bolus).

A number of sporadic changes were observed by 12-lead ECG and Holter monitor in studies N01256A and N01256B, but causality of brivaracetam was deemed unlikely.

Although Dr. Boehm did not make a definitive recommendation to approve or not approve the IV formulation, Dr. Yasuda found nothing that would preclude approval. The relative general safety of the oral drug helps support approval of the IV formulation. A total of 177 patients were exposed to the IV formulation, and patients were carefully monitored. Thus, the absence of a safety signal is reassuring here.

Dr. Hershkowitz further notes that demonstration of bioequivalence and similar bioavailability of the 2- to 15-minute IV infusions to the oral formulation further supports safety. Moreover, the lack of a cardiovascular signal associated with both IV and oral administration (even at very high doses in the QT studies) is reassuring. Drs. Hershkowitz and Dunn also opined that the IV formulation can be approved, and considering that IV injections will be performed by medical personal, the 2-minute bolus should be approved along with the 15-minute infusion.

# 9. Advisory Committee Meeting

Although brivaracetam is a new molecular entity, it is structurally related to levetiracetam, which has been approved since 1999. The clinical development program was not novel, the clinical trials were typical of those for other AEDs, and standard endpoints were evaluated. Lacking any controversial issues, and with clear evidence of efficacy and reasonable safety, we elected not to present this NDA to an advisory committee.

# 10. Pediatrics

The Applicant provided an initial pediatric study plan (iPSP), which was brought before the Pediatric Review Committee in September, 2014. The iPSP was agreed upon by the Division, the Pediatric Review Committee, and the Division of Pediatric and Maternal Health. A partial waiver was granted for the neonatal age group (birth to < 1 month) because studies are impossible or highly impracticable given the rarity of the diagnosis in this age group. The applicant had completed a pharmacokinetics study examining oral administration in pediatric patients 1 month and above. Thus, the iPSP provided the following information on planned studies (table from review of Dr. Sachs):

| Study | Description | Protocol submission | Study Initiation | Estimated Final Report Submission |
|---|---|---|---|---|
| N1266 | Long term open-label safety study (1 mo to <17 y) | Mar 2011 | (b) (4) | |
| (b) (4) | Double-blind, efficacy and safety study (1 mo to 4 years) | (b) (4) | | |
| (b) (4) | Intravenous PK and safety study (1 mo to (b) (4) years) | (b) (4) | | Jun 2020 |

Information abstracted from agreed upon iPSP Tables 5-1 and 10-1.

(b) (4)

In light of the above, study (b) (4) would not be necessary. All other studies are required. Adult and pediatric pharmacokinetics data must be submitted to identify a pediatric dosing regimen that provides the same exposure that has been found to be efficacious in adults.

## 11. Other Relevant Regulatory Issues

Not applicable.

## 12. Labeling

The main issues were:

- (b) (4) Because studies N01253 and N01358 were positive, the NDA provides substantial evidence of effectiveness. Based on the prospectively planned analysis, study N01252 was not positive, but given the effect size and the relevance of the doses studied, it seems appropriate to provide the results in Section14 (b) (4)
- Whether the IV formulation could be administered as a bolus injection as well as an infusion. The Division reached the conclusion that brivaracetam injection can be administered IV over 2 to 15 minutes (i.e., a slow bolus or an infusion).
- Whether the dosage should be reduced in patients with hepatic insufficiency. The Division reached the conclusion that for all stages of hepatic impairment, the recommended starting dosage should be 25 mg BID and the recommended maximum dosage should be 75 mg BID.
- What to say about concomitant treatment with levetiracetam. The label will say that in two of the efficacy studies (N01252 and N01253), ~20% of patients were on concomitant levetiracetam, and there was no observed benefit when brivaracetam was added to levetiracetam.

## 13. Postmarketing Recommendations

**Risk Evaluation and Management Strategies (REMS); Post-marketing Requirements**

A REMS was not determined to be necessary. There will be PMRs related to PREA, but no additional PMRs. See pediatrics section, above.

**Postmarketing Pharmacovigilance**

The applicant must provide postmarketing surveillance and enhanced pharmacovigilance for interstitial nephritis. All confirmed or possible cases of interstitial nephritis must be reported in an expedited fashion. The applicant should provide annual reports that provide a cumulative/synthesized analysis of all postmarketing cases of renal failure, interstitial nephritis and other reported alterations in renal function. The report should include an analysis of causality and information on pertinent laboratory values (serum creatinine, creatinine clearance, pertinent serum electrolytes, serum pH, and biopsy reports).

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

ELLIS F UNGER
02/18/2016