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APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA #/Supplement #	205836/205837/205838
Applicant Name	UCB
Date of Submission	11/24/14
PDUFA Goal Date	2/20/16
Proprietary Name/ Established (USAN) Name	Briviact/brivaracetam
Dosage Forms/Strength	Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg Intravenous injection: 50mg/5mL Oral solution: 10 mg/mL
Proposed Indication(s)	Adjunctive therapy in the treatment of partial-onset seizures in patients 16 years and older with epilepsy
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Cathy Michaloski, BSN, MPH, RAC
Medical Officer Review	Steve Dinsmore, DO; Mary Doi, MD; Jerry Boehm, MD
Statistical Review	Sharon Yan, PhD
Pharmacology Toxicology Review	Ed Fisher, PhD
CMC/OBP Review	Martha Heimann, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Michael Bewernitz, PhD; Xinning Yang, PhD
OPDP	Dhara Shah, PharmD
OSI	Antoine El Hage, PhD
CDTL Review	Norm Hershkowitz, MD, PhD
OSE/DMEPA	Justine Harris, BS, RPh
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	Nyedra Booker, PharmD
PMHS	Hari Sachs, MD
SEALD	N/A
Other	Marty Rusinowitz, MD (CSS)

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The applicant has provided substantial evidence of effectiveness for the use of brivaracetam as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years and older with epilepsy. This conclusion is supported by evidence from three adequate and well-controlled studies (studies 1252, 1253, and 1358) that evaluated the use of brivaracetam at various doses. These studies were all highly similar, differing primarily only in the doses evaluated in each study and in the concomitant use of a closely-related anticonvulsant, levetiracetam, known to be effective in the studied population. These studies were generally of typical design and evaluated the rather usual primary outcome of seizure frequency over the treatment period, comparing brivaracetam to placebo.

As noted, these studies differed in the doses each evaluated. Study 1358 evaluated daily doses of 100 mg and 200 mg. Similar highly statistically significant results were observed for both doses, reducing seizure frequency by about 25%. Study 1253 evaluated daily doses of 5 mg, 20 mg, and 50 mg. Only the 50 mg dose had a statistically significant result, reducing seizure frequency by about 17%. The 20 mg dose was not significant but had an observed numerical reduction of seizure frequency of 5%. Study 1252 evaluated daily doses of 20 mg, 50 mg, and 100 mg. In this study, the 50 mg dose was assessed first (somewhat inexplicably) in the statistical hierarchy, and, though it numerically reduced seizure frequency by about 10%, this result was not statistically significant, rendering the 17% reduction in seizure frequency of the 100 mg dose nominally, but not statistically, significant, as it was tested in the statistical hierarchy after the 50 mg dose failed to attain statistical significance. These primary effects on reduction in seizure frequency were supported by consistent effects on various secondary, subgroup, and sensitivity analyses.

Taken together, it is quite reasonable for these various doses assessed in studies of similar design and execution to provide mutual support for their observed effects. There is evidence to support daily doses ranging from 50 mg to 200 mg, although the evidence at 50 mg is somewhat less compelling than the higher doses. It appears an adequate range of doses was explored, as efficacy appears to fall off at doses below 50 mg and the two upper doses of 100 mg and 200 mg had similar effects.

Given the bioequivalence or highly comparable bioavailability of brivaracetam oral solution and intravenous injection compared to oral tablets, the effectiveness demonstrated in the studies of oral tablets may appropriately be conveyed to the oral solution and the intravenous injection.

There are no safety concerns in a database of acceptable size and character that preclude approval. The adverse event profile observed with brivaracetam appears generally consistent with that typically seen with antiepileptic drugs and no cases of unusual toxicities clearly attributable

to brivaracetam were observed. Neurologic events of somnolence, fatigue, and related symptoms, along with dyscoordination, as well as psychiatric symptoms, occasionally serious, of anxiety, depression, and, less commonly, aggression and psychosis, are most prominent. Hypersensitivity appears rare, but possible, and warrants mention. Suicidality, though recognized as a concern for the overall class of antiepileptic drugs, was actually less common in brivaracetam-treated patients in the controlled trials. A case of chronic interstitial nephritis is of uncertain relationship to brivaracetam.

Given the presence of substantial evidence of effectiveness and the acceptable safety profile, the risk benefit profile of brivaracetam is favorable and supports approval. Epilepsy is a serious and life-threatening condition, and we know that individual patients have significant variability in their response to various antiepileptic drugs, even if the studies demonstrating the effectiveness of those drugs appear to indicate similar benefits in the populations studied. Continued development and approval of antiepileptic drugs, hopefully ever more effective, but even if apparently consistent with preceding drugs, is important. The primary considerations are whether substantial evidence of effectiveness has been provided and whether the safety profile of the drug is acceptable in the setting of that evidence.

With regard to which doses to describe in labeling, the members of the review team are not in complete alignment. All agree that daily doses of 100 mg and 200 mg are effective and that doses below 50 mg should not be described. Dr. Yan feels that the effectiveness of a daily dose of 50 mg could not be conclusively demonstrated. Dr. Dinsmore and Dr. Hershkowitz argue that a daily dose of 50 mg should be described. Given the statistical significance of the 50 mg dose in one study, its numerical trend in another study, the overall pattern of benefit with various doses, the evidence suggesting no benefit at doses below 50 mg, and individual patient variability, I agree that we should include a dose of 50 mg in labeling. We will suggest a recommended starting dose of 100 mg daily but indicate that 50 mg daily may be considered.

A related issue is how to describe the doses from Study 1252 in labeling. After careful consideration, we have concluded that is appropriate to present the numerical results for both the 50 mg and 100 mg doses while noting that they are not statistically significant. Considered in the overall picture of all the studies, these numerical results are informative.

We will include in labeling a brief discussion of the data suggesting that there is no additional benefit of brivaracetam when added to levetiracetam. We will point out that these data come from a limited number of patients. We will also point out that a significant number of patients with prior exposure to levetiracetam were enrolled in a study that strongly demonstrated the effectiveness of brivaracetam.

While we will include in labeling the standard class language concerning suicidality, I note that the incidence of suicidality in controlled brivaracetam trials is actually less than it is for placebo.

A pharmacokinetic study to compare drug exposure in children 4 years and older with adults, a pharmacokinetic and safety study of the

intravenous formulation in pediatric patients 1 month to less than 16 years old, a study to determine the effectiveness and safety of brivaracetam in pediatric patients 1 month to less than 4 years old, and a long-term safety in pediatric patients 1 month to less than 16 years old will all be needed and will be conducted as postmarketing requirements.

There are no other postmarketing requirements or commitments.

Postmarketing risk management activities will include a request for the applicant to perform postmarketing surveillance and enhanced pharmacovigilance for interstitial nephritis with expedited reporting and summarized annual analysis of events.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of brivaracetam as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

For these reasons, I recommend approval of these applications, to include the agreed-upon product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Epilepsy is a serious condition with a spectrum of impacts on patients. At a minimum, even if seizures are well-controlled, epilepsy and its treatments have significant effects on daily life. At worst, and not uncommonly, epilepsy can be fatal.	New treatments are required.
Current Treatment Options	• Despite the availability of nearly 20 approved medications, epilepsy patients with partial-onset seizures can continue to experience recurrent seizures. About 35% of patients with partial-onset seizures do not achieve complete seizure control on currently available therapies.	There remains a pressing need for additional treatments.
Benefit	• Brivaracetam demonstrated a statistically significant or nominally significant benefit in reducing seizure frequency from baseline as compared to placebo in patients with refractory partial-onset seizures in the 3 primary studies supporting efficacy. A variety of doses were evaluated with a reduction in frequency in the 3 primary studies ranging from 17% to 26%. Additional efficacy analyses were supportive of these primary findings. Effective doses most clearly include 100 mg and 200 mg daily, with 50 mg daily also likely to be effective, though not	Effectiveness has been demonstrated at a variety of doses. Given the variable response in individual epilepsy patients, substantial benefit in particular individuals is likely to occur with clinical use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	quite as clearly demonstrated.	
Risk	• The adverse events that were primarily seen in the studies are generally typical of those seen with anticonvulsants. No particular pattern of unique toxicity was seen. Adverse events that did occur were generally reversible. A case of interstitial nephritis is of uncertain relationship to brivaracetam.	The adverse event profile appears largely consistent with a large number of approved anticonvulsants.
Risk Management	• Enhanced pharmacovigilance for interstitial nephritis will be requested. No other specific risk management is needed.	Safety concerns can likely be addressed through careful labeling and pharmacovigilance.

2. Background

Brivaracetam (BRV) is not an approved drug product for any indication and has not previously been the subject of any marketing application. It is a new molecular entity intended to be used as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

Epilepsy is a well-known and common condition, typically resulting in seizures of various types in those so afflicted, with partial-onset seizures occurring in most. Though numerous medications have been approved for partial-onset epileptic seizures, a substantial number of patients with epilepsy continue to have incomplete seizure control, and there can be considerable variability in individual responses to these different medications.

BRV is similar the approved antiepileptic drug (AED) levetiracetam (LEV), a drug effective in multiple seizure types. LEV is approved for partial-onset, myoclonic, and primary generalized tonic-clonic seizures. Although the precise mechanism of action of LEV is unknown, binding to the synaptic vesicle protein SV2A may be involved in its antiepileptic effect. BRV binds to SV2A much as LEV does, though with even higher affinity, and in light of its structural similarity to LEV, it is reasonable to assume that SV2A binding may also be involved in the antiepileptic effect of BRV.

The applicant is UCB. UCB is an established company in the development of epilepsy drugs, marketing both LEV and another AED, lacosamide. The Division was involved throughout the development of BRV, and Dr. Dinsmore has a detailed presentation in his review of the regulatory history and interactions with UCB. Selected important issues of discussion during development included adequate dose exploration, concomitant AED exposure, and endpoint selection.

This overall submission consists of three technically distinct applications for three dosage forms. The applicant proposes the approval of oral tablets based on the results of clinical efficacy and safety studies, an intravenous injection based on bioavailability/bioequivalence and safety studies, and an oral solution based on bioavailability/bioequivalence studies.

The members of the review team recommend approval and I will briefly discuss their major findings.

3. Product Quality

I concur with the conclusions reached by Dr. Heimann regarding the acceptability of the manufacturing of the drug product and drug substance for the tablets, intravenous injection, and oral solution. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no postmarketing commitments or requirements. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Dr. Fisher that there are no outstanding pharmacology/toxicology issues that preclude approval. Though Dr. Fisher raised the issue of additional postmarketing assessment of reproductive and developmental toxicity due to possible improper dose selection in the completed studies, I note Dr. Lois Freed's comments in her supervisory memo that, based on the data submitted, higher plasma exposures, sufficient to warrant repeat reproductive and developmental toxicity studies, would not have been achieved at doses that would have been tolerated. Accordingly, she does not recommend postmarketing requirements for repeat reproductive and developmental toxicity studies as a condition of approval.

5. Clinical Pharmacology

I concur with the conclusions reached by Dr. Bewernitz and Dr. Yang that there are no outstanding clinical pharmacology issues that preclude approval. Their review discusses the usual pharmacokinetic (PK) considerations. Dr. Hershkowitz has summarized these in his memo. Selected findings include:

- Exposure-response analyses support adequate dose exploration, with a range of effective doses from 50 mg to 200 mg daily.
- Exposure-response analyses suggest no additional benefit from BRV in patients on LEV.
- Exposure-response analyses for common safety findings were flat at the proposed doses.
- No dose adjustment is required in subjects with renal impairment.
- The clinical pharmacology team suggests that no dose adjustment is required for patients with hepatic impairment, despite increases in BRV exposure of 50-60% in study subjects with varying degrees of hepatic impairment, because adverse events seen at 100 mg daily and 200 mg daily were similar. Dr. Hershkowitz mildly disagrees, arguing that a reduction in maximum dose to 150 mg daily is advisable, based on the limited information available at higher doses, small number of subjects evaluated, short duration of exposure, and consistency with typical approaches to other anticonvulsants. This is reasonable and we have incorporated recommendations for dose reduction in hepatic impairment in labeling.
- Dose adjustments are not required for age, gender, or race.
- BRV dosing should be doubled with concomitant rifampin.
- Monitoring for tolerability and consideration of carbamazepine (CBZ) dose reduction should be considered with concomitant use of CBZ.

- Phenytoin levels may be slightly altered and should be monitored when used concomitantly with BRV.

- No dose adjustment is needed for oral contraceptives.

- BRV can be administered without regard to meals.

- There was no significant QT prolongation at BRV doses up to 800 daily.

- BRV oral tablets and oral solution are bioequivalent.

- BRV oral tablets and intravenous injection are either bioequivalent or have highly comparable bioavailability, depending on the rapidity of injection, and dose adjustments when switching between dosage forms are not necessary. Although Cmax is increased with bolus injection compared to oral administration, use of this approach was well tolerated and will be performed in monitored inpatients settings.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

As discussed by Dr. Yan, Dr. Dinsmore, and Dr. Hershkowitz, 3 studies of similar design provide the primary data intended to support efficacy, which I shall refer to as Studies 1, 2, and 3 (studies 1252, 1253, and 1358, respectively). I will briefly discuss these studies and refer to the team's reviews for additional detailed discussion.

As Dr. Hershkowitz and other members of the review team note, these studies were parallel, fixed-dose, randomized, double-blind, placebo-controlled studies that enrolled patients with refractory partial onset seizures (POS), with or without secondary generalization. Enrollment criteria are summarized in the various reviews. Patients were adults with ongoing recurrent seizures despite stable concomitant treatment. Concomitant use of LEV in Study 1 and 2 was limited to a maximum of 20% of enrolled patients. It was not allowed in Study 3. Studies 2 and 3 included patients from North America. Patients from the United States constituted approximately 20% of the total combined population of all 3 studies. Enrollment was stratified by geographic area, LEV use (current in Studies 1 and 2; historical in Study 3), and, in Study 3, number of previous AEDs.

Eligible subjects were enrolled and began an 8 week baseline period of assessment to establish seizure frequency. Those subjects having 8 POS during the baseline period were randomized equally to the various treatment groups and began full dose treatment for the 12 week treatment period. Doses evaluated in the studies ranged from 20 mg to 200 mg daily, given in

divided doses twice a day. Study 1 evaluated daily doses of 20 mg, 50 mg, and 100 mg. Study 2 evaluated daily doses of 20 mg and 50 mg. Study 3 evaluated daily doses of 100 mg and 200 mg. The treatment period was used in the calculation of the primary efficacy outcome, but patients could subsequently continue or stop treatment in a protocol-defined manner.

Few patients discontinued, with a high retention rate of patients in the 3 studies of about 90% in both the active and placebo groups. Discontinuation was generally due to adverse events. There were minimal missing data. Patients in the various arms of the studies were well-matched on demographic characteristics.

The primary outcome measure in all 3 studies was the seizure frequency over the treatment period. The seizure frequency was described per 7 days in Studies 1 and 2 and per 28 days in Study 3. The occurrence of seizures was recorded on a standardized "daily record card" that documented the date, number, and type of reported seizures. The primary analysis was performed on the usual modified intent to treat population consisting of all patients who received at least a single dose and who had a measurable outcome. The primary analysis did not include 4 patients in Study 3 that were excluded from a single site because of site noncompliance with regulatory guidelines and requirements and protocol violations. Dr. Yan included these excluded patients in a sensitivity analysis and found little effect attributable to their exclusion. Dr. Yan also submitted an addendum to her review correcting a mathematical error found in the applicant's calculations of the percent seizure reduction. The results reported in the reviews of Dr. Dinsmore and Dr. Hershkowitz (and below) reflect this correction.

The following table from page 31 of Dr. Dinsmore's review summarizes the characteristics of these 3 studies:

Study number	# subjects	LEV use[1]		Study Characteristics	Age range	patients / treatment Arm	Treatment Period (= maintenance period)	1º Efficacy variable
		Yes	No					
N01252	398	76	322	Multi-center, multinational double blind, parallel group, placebo controlled, randomized	≥16 to 70	PBO= 100 20mg/day= 99 50mg/day= 99 100mg/day= 100	Treatment period= 12 weeks	POS[2] frequency /week (7 days) over treatment period
N01253	396	76	320	Multi-center, multinational double blind, parallel group, placebo controlled, randomized	≥16 to 70	PBO= 98 20mg/day= 100 50mg/day= 101	Treatment period= 12 weeks	POS[2] frequency /week (7 days) over treatment period
N01358	764	Concomitant LEV excluded		Multi-center, multinational double blind, parallel group, placebo controlled, randomized	≥16 to 80	PBO= 261 100mg/day= 253 200mg/day= 250	Treatment period= 12 weeks	POS[2] frequency /28 days over treatment period

[1]LEV= levetiracetam
[2]POS= partial onset seizures

The following tables taken from pages 13, 14, and 15 of Dr. Hershkowitz's review summarize the primary outcome findings for Studies 1, 2, and 3.

Study 1

	Placebo N=100	BRV		
		20 mg/day N=99	50 mg/day N=99	100 mg/day N=100
Baseline median seizure frequency*	2.07	1.93	1.80	2.02
Treatment median seizure frequency*	1.75	1.34	1.49	1.26
Adjusted Mean Percent Reduction in Seizure Frequency over Placebo		9.9	9.5	17.0
Primary analysis LS mean % reduction (95% CI) p-value	2.21	 1.99 6.8 (-4.8, 17.1) 0.239	 2.00 6.5 (-5.2, 16.9) 0.261	 1.84 11.7 (0.7, 21.4) 0.037
Sensitivity analysis-mixed effect LS mean % reduction (95% CI) p-value	1.77	 1.57 7.4 (-3.6, 17.3) 0.178	 1.66 3.9 (-7.5, 14.2) 0.484	 1.52 8.9 (-1.9, 18.5) 0.104
Sensitivity analysis- ranks p-value		 0.174	 0.246	 0.021

*The frequency value is based upon the protocol driven endpoint of #seizures/7days.

Note that nominal statistical significance is only achieved for the 100 mg dose. Note also, though, that contrary to the usual approach of evaluating doses in a statistically valid manner from high to low (advice we routinely share with sponsors), in Study 1 the applicant's statistical plan specified consideration of the 50 mg dose prior to the 100 mg dose. Thus, while all doses suggest a numerical benefit in seizure frequency reduction over placebo, none may be considered statistically significant. This is discussed at great length in the reviews of Dr. Yan, Dr. Dinsmore, and Dr. Hershkowitz. Dr. Hershkowitz points out that the sensitivity analyses conducted to allow for the non-normal distribution of data in the study support the nominal importance of the primary analysis of the 100 mg dose. Dr. Yan notes that the analysis of 50% responder rate, a secondary outcome, may only be considered for descriptive purposes (given the failed primary analysis, none of the secondary endpoints were eligible for statistical testing) but was supportive as the 100 mg group compared to placebo group reached nominal significance with a p-value of 0.023. There appears to be evidence of dose-response between the 50 mg and 100 mg groups, although the 20 mg group was essentially the same as the 50 mg group.

Study 2

	Placebo N=96	BRV		
		5 mg/day N=96	20 mg/day N=99	50 mg/day N=101
Baseline median seizure frequency*	2.63	2.32	2.23	2.85
Treatment median seizure frequency*	2.15	1.80	1.96	1.70
Adjusted Mean Percent Reduction in Seizure Frequency over Placebo		-1.2	5.4	16.9
Primary analysis LS mean % reduction (95% CI) p-value	3.13	3.17 -0.9 (-13.9, 106) 0.885	2.96 4.1 (-8.1, 15.0) 0.492	2.60 12.8 (1.7, 22.6) 0.025
Sensitivity analysis-mixed effect LS mean % reduction (95% CI) p-value	2.65	2.47 4.8 (-7.8, 16.0) 0.437	2.36 7.9 (-4.1, 18.6) 0.189	2.07 15.9 (4.9, 25.6) 0.006
Sensitivity analysis- ranks p-value		0.698	0.303	0.003

*The frequency value is based upon the protocol driven endpoint of #seizures/7days.

In Study 2, statistical significance was achieved for the 50 mg dose. In this study, sequential analysis proceeded from high to low, as is typical. Accordingly, the finding for the 50 mg dose group is statistically valid. Sensitivity analyses were supportive of this finding. The other two dose groups were not significant. A consistent pattern of dose-response is apparent.

Study 3

	Placebo N=259	BRV	
		100 mg/day N=252	200 mg/day N=249
Baseline median seizure frequency*	10.0	9.5	9.3
Treatment median seizure frequency*	8.7	6.3	5.8
Adjusted Mean Percent Reduction in Seizure Frequency over Placebo		25.2	25.9
Primary analysis LS mean seizure freq per 28 days (seizure frequency per week) % reduction (95% CI) p-value	9.2 (2.3)	6.9 (1.7) 22.8 (13.3, 31.2) <.001	6.8 (1.7) 23.2 (13.8, 31.6) <.001
Non-parametric rank ANCOVA p-value		<.001	<.001
EU primary outcome, 50% respond Responders, n (%) Odds ratio[1] p-value	56 (21.6)	98 (38.9) 2.39 <.001	94 (37.8) 2.19 <.001

**The frequency value is based upon the protocol driven endpoint of #seizures/28 days.

In Study 3, both the 100 mg and 200 mg groups reached statistical significance. The 50% responder rate was similarly significant. No dose-response is apparent.

Additional subgroup explorations reported by Dr. Yan and Dr. Dinsmore did not suggest substantial differences from the primary and major secondary findings. Dr. Yan notes that subgroup analyses by demographic characteristics were relatively consistent with the primary findings. Dr. Dinsmore performed various additional analyses intended to consider the potential for loss of treatment effect over time or paradoxical worsening of seizures. No such indications were observed.

Dr. Dinsmore and Dr. Yan also investigated the potential for an impact of concomitant use of LEV or CBZ on effects of BRV. BRV increases the active metabolite of CBZ but no suggestion of a clinically evident interaction was observed. Given that BRV and LEV share the same putative mechanism of action, Dr. Dinsmore and Dr. Yan explored data from Study 1 and Study 2, studies in which a subset of patients were allowed to be treated with concomitant LEV, and found some suggestion that seizures may have been reduced when LEV was not present as a concomitant medication but may have been slightly increased in the presence of concomitant LEV. The data suggesting such effects are seen in this table that Dr. Dinsmore prepared and Dr. Hershkowitz includes in his review on page 16.

TREATMENT ARM	1252-1253, LEV-NO LEV	Number of patients	Median Treatment Sz Frequency	Effect
PBO	CON LEV	37	8.28	
PBO	NO LEV	159	7.53	
5mg	CON LEV	18	10.66	-2.38
5mg	NO LEV	78	6.91	0.62
20mg	CON LEV	37	8.68	-0.4
20mg	NO LEV	161	5.63	1.9
50mg	CON LEV	39	9.14	-0.86
50mg	NO LEV	161	5.63	1.9
100mg	CON LEV	20	9.76	-1.48
100mg	NO LEV	80	4.48	3.05

Though Dr. Hershkowitz points out that the data are limited and exploratory, they appear consistent with the ostensibly shared mechanism of action of the two drugs. I note that the clinical pharmacology review observed that exposure-response analyses suggested no additional benefit from BRV in patients on LEV.

As noted above, BRV oral tablets and oral solution are bioequivalent, and BRV oral tablets and intravenous injection are either bioequivalent or have highly comparable bioavailability. Any effectiveness demonstrated for BRV oral tablets may be appropriately conveyed to BRV oral solution and BRV intravenous injection.

Overall, the review team recommends approval, though Dr. Yan's opinion differs slightly those of Dr. Dinsmore and Dr. Hershkowitz. All agree that there is strong evidence supporting the effectiveness of the 100 mg and 200 mg doses. All appear willing to accept the nominal significance of the 100 mg dose in Study 1, despite its location in the sequential testing procedure after a failed dose. Given the similar responses obtained with the 100 mg and 200

mg doses in Study 3, the review team recommends an initial dose of 100 mg with consideration of an escalation to 200 mg in patients who might benefit from improved seizure control and can tolerate the higher dose. Dr. Yan is not impressed with the 50 mg dose, noting that statistical significance was reached in Study 2, but not in Study 1, and that BRV at doses below 50 mg did not show effectiveness. Dr. Dinsmore and Dr. Hershkowitz take a somewhat more charitable view, noting that the 50 mg dose was positive in one trial and suggesting that it might be worthwhile to recommend a trial of the 50 mg dose in patients unable to tolerate the 100 mg dose. All favor inclusion in labeling of information regarding the concomitant use of LEV.

8. Safety

As discussed in the reviews of Dr. Doi and Dr. Boehm, there are no safety issues associated with the use of BRV that would preclude approval. In addition to their detailed discussion of safety findings, Dr. Yasuda provides a thorough secondary review of the safety findings and Dr. Hershkowitz summarizes the safety findings and issues in his memo. I will briefly consider the major issues they have discussed.

The size of the safety database was adequate. Safety assessments were deemed generally adequate by the review team. Dr. Boehm points out that the intravenous safety data come from a relatively small total number of subjects, the exposures were brief, and there is no placebo comparison group available for direct comparisons. There was considerable exposure to doses within the proposed dosing range of 50 mg to 200 mg daily. Similarly, there was substantial exposure in epilepsy patients. A large portion of the exposure comes from the randomized, double-blind, placebo-controlled epilepsy studies discussed above.

There were 44 deaths reported in the application. Although 35 were in the POS studies (9 were in other indications), only 6 occurred in the controlled epilepsy studies, with 5 in BRV patients and 1 in a placebo patient. Of the 5 deaths in BRV patients, 3 were cases of definite sudden unexpected death in epilepsy (SUDEP), thought to generally be related to the underlying epilepsy and for which treatment with effective AEDs is thought to be somewhat protective. In addition, 2 of these 3 had been off of BRV for a period ranging from 9 to 14 days, further suggesting that BRV was not related. The other 2 deaths in BRV patients in epilepsy trials were a case of respiratory failure after a witnessed seizure and a death due to drowning after diving into a river. There were a variety of other deaths that occurred in uncontrolled settings. They are presented and summarized in the various reviews. All review team members agree that there is no evidence to draw any definitive conclusions regarding the role of BRV in the various deaths reported in the application. I have reviewed these cases, also, and I agree with the team.

Regarding SUDEP, Dr. Doi calculated a rate lower than that reported for the refractory epilepsy population. Accordingly, the review team agrees with Dr. Doi that BRV does not appear to be associated with an increased risk for SUDEP.

Although serious adverse events were few in number and balanced between BRV and placebo subjects, Dr. Doi, Dr. Boehm, Dr. Yasuda, and Dr. Hershkowitz have discussed safety concerns of interest thoroughly in their comprehensive and summary reviews. Main findings include:

Neurologic Symptoms
These are very common, and, in fact, generally expected, with AED use. Indeed, here we see a slight preponderance of these common symptoms in the BRV group as compared to placebo (39% at proposed doses vs. 29%). The symptoms themselves are typical of AEDs – somnolence, fatigue, dizziness (and all its attendant variants), dyscoordination, and nystagmus. Although we are familiar with such events, the team recommends including a description in Section 5 of labeling given their frequency and correspondence with a small number of discontinuations. This is reasonable. Dr. Hershkowitz also agrees this is reasonable, but points out that he suspects the incidence of these symptoms is actually lower than with other AEDs.

Falls and Injuries
Although Dr. Doi argues that a slight preponderance of falls and injuries occurred in BRV patients when compared to placebo and recommends inclusion in Section 5, Dr. Yasuda and Dr. Hershkowitz reject this, noting small differences, confounding effects of seizures themselves, and inconsistencies in the data. I agree the signal is not impressive.

Psychiatric Symptoms
We will include the standard class labeling for suicidality in Section 5, though it is interesting that the incidence of suicidality in controlled BRV trials is actually less than it is for placebo. Other psychiatric symptoms, some serious, and driven primarily by anxiety and depression, were more common in BRV (13%) than placebo (8%). There were also several cases of psychosis and/or hostility/aggression that were temporally related to BRV initiation and had positive dechallenge in patients without a history of psychiatric disorder. Overall, the team, influenced in some part by the fact that LEV includes labeling for psychosis and psychiatric effects in Section 5, favors the same approach for BRV. This is not an unreasonable stance.

Hypersensitivity
Although there may be a very small preponderance in BRV patients of general hypersensitivity events using broad terms (fractions of a percent), Dr. Doi identified a case in the uncontrolled epilepsy database of a BRV patient developing angioedema, and another case of sudden dyspnea, both of which responded to drug discontinuation. After some discussion, the team feels these cases warrant description in Section 5, with careful attention to accurate description as “bronchospasm and angioedema” rather than anaphylaxis.

Renal Disorders
In addition to some nonspecific renal events not clearly attributable to drug, the primary issue here concerns a single case of tubulointerstitial nephritis, confirmed by biopsy, that did not resolve after drug discontinuation. No other information is available and it remains unexplained. Dr. Doi recommends postmarketing surveillance/enhanced pharmacovigilance

for chronic interstitial nephritis as BRV causality could not be ruled out. Both Dr. Yasuda and Dr. Hershkowitz agree.

Dr. Hershkowitz and Dr. Yasuda have provided summaries of Dr. Doi's detailed presentation of common adverse event, laboratory, and vital sign data, and I refer to their summaries for further discussion.

Dr. Boehm reviewed the safety data from the intravenous studies and, noting that the studies were small, of short duration, and lacked a placebo comparator, found nothing to distinguish the intravenous injection from the oral formulation, other than non-BRV-specific injection-related issues. Dr. Yasuda notes that there are no safety issues associated with intravenous use that preclude approval. Dr. Hershkowitz agrees with approval of the intravenous formulation with options for both rapid and slow administration, noting the clinical pharmacology findings presented above, the lack of any convincing cardiovascular signal, and its anticipated use by trained medical staff in a monitored setting.

There is no foreign marketing experience.

Overall, Dr. Doi, Dr. Boehm, Dr. Yasuda, and Dr. Hershkowitz all find no safety issues that would preclude approval. No post-marketing requirements are needed. Labeling will include appropriate Warnings as discussed above. Consideration will be given to enhanced postmarketing surveillance for chronic interstitial nephritis. A REMS is not required for this application.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of partial-onset seizures in patients with epilepsy and because the clinical trial design is similar to that of trials of previously approved drugs for the treatment of partial-onset seizures in patients with epilepsy.

10. Pediatrics

(b) (4)

This approach was presented to PeRC on November 18, 2015, in the form of a revised pediatric plan for BRV. The plan will include the following POS studies (as noted in the review of Dr. Sachs) that PeRC has agreed to:

- Pharmacokinetic and safety study (4 years of age and older)
- Efficacy study (1 month to 4 years of age)
- Long-term safety study (1 month of age and older)

These studies will be postmarketing requirements under PREA.

We will issue a partial waiver for the neonatal age group (birth to less than 1 month of age) because studies are impossible or highly impracticable in neonates because there are too few children with confirmed epilepsy in this age group.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Postmarketing

As noted above, the members of the review team agree that a REMS is not required for this application. I agree.

Postmarketing requirements and commitments, and related issues, include a requirement for the pediatric studies noted above. There are no other postmarketing requirements or commitments.

We will request postmarketing surveillance and enhanced pharmacovigilance for interstitial nephritis.

14. Decision/Action/Risk Benefit Assessment

The applicant has provided substantial evidence of effectiveness for the use of brivaracetam as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years and older with epilepsy. This conclusion is supported by evidence from three adequate and well-controlled studies (studies 1252, 1253, and 1358) that evaluated the use of brivaracetam at various doses. These studies were all highly similar, differing primarily only in the doses evaluated in each study and in the concomitant use of a closely-related anticonvulsant, levetiracetam, known to be effective in the studied population. These studies were generally of typical design and evaluated the rather usual primary outcome of seizure frequency over the treatment period, comparing brivaracetam to placebo.

As noted, these studies differed in the doses each evaluated. Study 1358 evaluated daily doses of 100 mg and 200 mg. Similar highly statistically significant results were observed for both doses, reducing seizure frequency by about 25%. Study 1253 evaluated daily doses of 5 mg, 20 mg, and 50 mg. Only the 50 mg dose had a statistically significant result, reducing seizure frequency by about 17%. The 20 mg dose was not significant but had an observed numerical reduction of seizure frequency of 5%. Study 1252 evaluated daily doses of 20 mg, 50 mg, and 100 mg. In this study, the 50 mg dose was assessed first (somewhat inexplicably) in the statistical hierarchy, and, though it numerically reduced seizure frequency by about 10%, this result was not statistically significant, rendering the 17% reduction in seizure frequency of the 100 mg dose nominally, but not statistically, significant, as it was tested in the statistical hierarchy after the 50 mg dose failed to attain statistical significance. These primary effects on reduction in seizure frequency were supported by consistent effects on various secondary, subgroup, and sensitivity analyses.

Taken together, it is quite reasonable for these various doses assessed in studies of similar design and execution to provide mutual support for their observed effects. There is evidence to support daily doses ranging from 50 mg to 200 mg, although the evidence at 50 mg is somewhat less compelling than the higher doses. It appears an adequate range of doses was explored, as efficacy appears to fall off at doses below 50 mg and the two upper doses of 100 mg and 200 mg had similar effects.

Given the bioequivalence or highly comparable bioavailability of brivaracetam oral solution and intravenous injection compared to oral tablets, the effectiveness demonstrated in the studies of oral tablets may appropriately be conveyed to the oral solution and the intravenous injection.

There are no safety concerns in a database of acceptable size and character that preclude approval. The adverse event profile observed with brivaracetam appears generally consistent with that typically seen with antiepileptic drugs and no cases of unusual toxicities clearly attributable to brivaracetam were observed. Neurologic events of somnolence, fatigue, and related symptoms, along with dyscoordination, as well as psychiatric symptoms, occasionally serious, of anxiety, depression, and, less commonly, aggression and psychosis, are most

prominent. Hypersensitivity appears rare, but possible, and warrants mention. Suicidality, though recognized as a concern for the overall class of antiepileptic drugs, was actually less common in brivaracetam-treated patients in the controlled trials. A case of chronic interstitial nephritis is of uncertain relationship to brivaracetam.

Given the presence of substantial evidence of effectiveness and the acceptable safety profile, the risk benefit profile of brivaracetam is favorable and supports approval. Epilepsy is a serious and life-threatening condition, and we know that individual patients have significant variability in their response to various antiepileptic drugs, even if the studies demonstrating the effectiveness of those drugs appear to indicate similar benefits in the populations studied. Continued development and approval of antiepileptic drugs, hopefully ever more effective, but even if apparently consistent with preceding drugs, is important. The primary considerations are whether substantial evidence of effectiveness has been provided and whether the safety profile of the drug is acceptable in the setting of that evidence.

With regard to which doses to describe in labeling, the members of the review team are not in complete alignment. All agree that daily doses of 100 mg and 200 mg are effective and that doses below 50 mg should not be described. Dr. Yan feels that the effectiveness of a daily dose of 50 mg could not be conclusively demonstrated. Dr. Dinsmore and Dr. Hershkowitz argue that a daily dose of 50 mg should be described. Given the statistical significance of the 50 mg dose in one study, its numerical trend in another study, the overall pattern of benefit with various doses, the evidence suggesting no benefit at doses below 50 mg, and individual patient variability, I agree that we should include a dose of 50 mg in labeling. We will suggest a recommended starting dose of 100 mg daily but indicate that 50 mg daily may be considered.

A related issue is how to describe the doses from Study 1252 in labeling. After careful consideration, we have concluded that is appropriate to present the numerical results for both the 50 mg and 100 mg doses while noting that they are not statistically significant. Considered in the overall picture of all the studies, these numerical results are informative.

We will include in labeling a brief discussion of the data suggesting that there is no additional benefit of brivaracetam when added to levetiracetam. We will point out that these data come from a limited number of patients. We will also point out that a significant number of patients with prior exposure to levetiracetam were enrolled in a study that strongly demonstrated the effectiveness of brivaracetam.

While we will include in labeling the standard class language concerning suicidality, I note that the incidence of suicidality in controlled brivaracetam trials is actually less than it is for placebo.

A pharmacokinetic study to compare drug exposure in children 4 years and older with adults, a pharmacokinetic and safety study of the intravenous formulation in pediatric patients 1 month to less than 16 years old, a study to determine the effectiveness and safety of brivaracetam in pediatric patients 1 month to less than 4 years old, and a long-term safety in pediatric patients 1 month to less than 16 years old will all be needed and will be conducted as postmarketing requirements.

There are no other postmarketing requirements or commitments.

Postmarketing risk management activities will include a request for the applicant to perform postmarketing surveillance and enhanced pharmacovigilance for interstitial nephritis with expedited reporting and summarized annual analysis of events.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of brivaracetam as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

For these reasons, I recommend approval of these applications, to include the agreed-upon product labeling.

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

/s/

WILLIAM H Dunn
02/18/2016