Cross-Discipline Team Leader Review

Date	April 13, 2018
From	Teresa Buracchio, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	205836(S-5) 205838 (S-3)
Applicant	UCB
Date of Submission	7/10/2017
PDUFA Goal Date	5/10/2018
Proprietary Name / Non-Proprietary Name	Briviact (brivaracetam)
Dosage form(s) / Strength(s)	Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg; 10 mg/mL oral solution; 50 mg/5 mL single-use vial for intravenous use
Applicant Proposed Indication(s)/Population(s)	Treatment of partial-onset seizures patients 4 years of age and older
Recommendation on Regulatory Action	Approval

1. Background

Briviact (brivaracetam) tablet, oral solution, and injection formulations were approved for "adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older" on February 18, 2016. The sponsor subsequently received an approval to include a description in labeling of monotherapy dosing of Briviact for all formulations in the same indication and population on September 14, 2017, based on extrapolation from its approved adjunctive dosing regimen. Brivaracetam displays a high and selective affinity for brain-specific binding site synaptic vesicle protein 2A (SV2A), which may contribute to the its anticonvulsant activity.

This supplemental application seeks to extend the current indication for the treatment of partial-onset seizures (POS) to include pediatric patients down to 4 years of age based on pediatric extrapolation. The submission is intended to support both monotherapy and adjunctive dosing of Briviact tablets and oral solution in this population. Additional safety data will be required to support this indication for Briviact injection. The supplement addresses several Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs).

The Division of Neurology Products (DNP) issued a General Advice letter on November 12, 2015, indicating that it is acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of POS in adults. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and adults and on an analysis of multiple antiepileptic drugs, conducted by the FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS. Extrapolation based on this analysis applies only to POS in pediatric patients 4 years of age and older, and not to POS in pediatric patients 1 month of age to less than 4 years of age or to other forms of epilepsy. The following is required to support an indication for the treatment of POS in patients 4 years and older that relies upon extrapolation:

- Approved indication for the treatment of POS in adults.
- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis requires pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
- Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.

Additionally, DNP also issued a General Advice letter on September 13, 2016, indicating that it is acceptable to extrapolate monotherapy use of a drug approved as adjunctive use for the treatment of POS. To support use as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. To support extrapolation, the sponsor must provide pharmacokinetic information adequate to demonstrate such similarity, taking

into consideration possible drug-drug interactions (inhibition or induction) that may alter the metabolism of the drug.

A Type B pre-NDA meeting was held with the sponsor on March 9, 2017, to specifically discuss the contents of this submission to support pediatric dosing of Briviact for POS patients aged 4 to <16 years.

2. Product Quality

No new product quality information was submitted.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by reviewers Dr. M. Bewernitz and Dr. D. Li with Team Leaders Dr. K. Krudys and Dr. A. Men.

The following studies provided pediatric pharmacokinetic (PK) data with brivaracetam (BRV) for this application:

- Study N01263 – an open-label, single-arm, multicenter, dose-titration study to investigate the safety, tolerability and pharmacokinetics of brivaracetam in patients with epilepsy age ≥ 1 month to <16 years.
- Study N01266 – an open-label, multicenter, long-term extension study to obtain long-term safety and efficacy data of brivaracetam in pediatric subjects with epilepsy ≥ 1 month to <17 years. The study enrolled patients from N01263 and also directly enrolled pateints 4 to <17 years of age with focal seizures.

The following population PK analyses were used to determine a dosing regimen that would provide similar BRV exposures in pediatric subjects 4 years of age and older to those that were found to be effective in adult subjects with POS.

- CL0187 and CLO187 Amended Report: Population pharmacokinetic (PK) analysis of oral BRV in pediatric patients based on Study N01263. The initial report used an adult exposure reference range based on an adult population PK model (described in previously-submitted report N01328) which included adult PK data from Phase 2 and Phase 3 studies. The amended report included additional data from pivotal adult adjunctive BRV POS study N01358, which assessed 50 mg twice daily and 100 mg twice daily, that came in after CL0187 was complete.
- CL0258: Report CL0258 describes exposure-response modeling of BRV as an adjunctive therapy in children age ≥ 4 to <16 years with POS.

Please refer to the OCP review for a detailed description of the population PK models.

As described in the OCP review, the applicant performed simulations to inform pediatric dose selection using a 100 mg twice daily dose in adults as a target maximum exposure for pediatric dosing. PK simulations were conducted for a monotherapy setting. The average steady-state concentration ($C_{av,ss}$) was the exposure metric selected for the PK simulations. PK profiles were simulated for virtual pediatric patients using the pediatric PK model. Data from the NHANES database was used for the pediatric age and weight distribution.

Based on these analyses, the applicant proposed the following dosing regimen for pediatric patients:

Age and Body Weight	**Initial Dosage**	**Minimum and Maximum Maintenance Dosage**
Pediatric patients weighing 50 kg or more	25 mg twic daily	25 mg to 100 mg twice daily
Pediatric patients weighing less than 50 kg	0.5 mg/kg twice daily	0.5 to 2 mg/kg twice daily

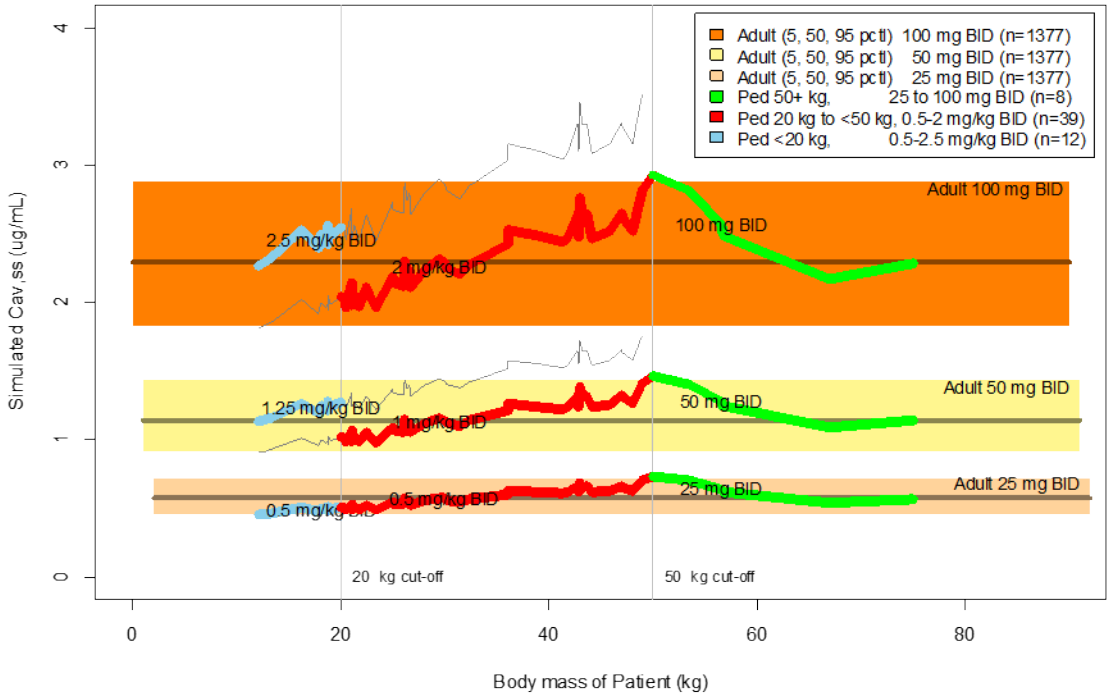
However, OCP noted that the proposed doses may lead to underexposure in lower weight patients. In a Type C meeting dated May 1, 2017, the Agency had previously advised the sponsor that an increase up to 2.5 mg/kg BID in pediatric patients may be warranted.

Maintenance Dose

OCP conducted independent PK simulations using the full range of approved adult maintenance dose levels (25, 50, and 100 mg BID) to inform pediatric dose selection. OCP also explored different weight "cut-offs" for increasing the dose for lighter patients and identified a body weight of 20 kg as a reasonable breakpoint to match adult exposures.

Figure 1, below, copied from the OCP review, shows the simulated exposures in pediatric patients using OCP's proposed dose range.

Figure 1. ***Simulated $C_{av,ss}$ in Pediatric Patients Based on Body Weight and Dose Using OCPs Proposed Maintenance Dosing and OCP's Proposed 20 kg Weight-Cut off Compared with Simulated $C_{av,ss}$ in Adult Patients at Approved Maintenance Doses***



Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated Cav,ss at the approved adult maintenance doses of 25, 50, and 100 mg BID. The curves represent the median simulated Cav,ss for a given body weight and maintenance dose. These simulations do not include between subject variability (e.g., all elements of the omega matrix are set to zero). The vertical line at 20 kg is included to visualize the cut-off weight for increasing the mg/kg dose for low body weight pediatric patients.

Based on these analyses, OCP recommends the following maintenance doses for both monotherapy and adjunctive use of BRV:

Patients 11 to < 20 kg: 0.5 to 2.5 mg/kg BID
Patients 20 to < 50 kg: 0.5 to 2 mg/kg BID
Patients ≥ 50 kg: 25 to 100 mg BID

The upper dose limit in ongoing study N01266 was increased from 2.0 to 2.5 mg/kg BID in protocol amendment 4. The interim report indicates that n = 96 patients were treated with a modal dose ≥ 2.0 mg/kg BID. It is possible that the 2.5 mg/kg BID dose level was administered to patients prior to completion of the interim report; however, there is no specific mention of the 2.5 mg/kg BID dose level in the interim report. Although it is unclear if lower weight patients receieved doses of 2.5 mg/kg BID in study N01266, the safety of this dose is supported by the 2.0 mg/kg BID dose in pediatric patients > 20 kg which is expected to provide similar exposures.

The lowest weight patient who provided clinical data for the age range was 11.0 kg and this lower weight limit will be described in the label.

Initial dose:
The PK simulations that were used for $C_{av,ss}$ can be used to inform the single-dose $C_{av.}$

The initial dose for adult patients is 50 mg BID, which may be increased to 100 mg BID or decreased to 25 mg BID based on efficacy and tolerability. The 50 mg BID dose allows patients to start at a therapeutic dose without titration. The applicant proposed an initial dose of 25 mg BID for patients weighing ≥ 50 kg and 0.5 mg/kg BID for patients weighing <50 kg. Those initiation doses were used in Study N01263 and Study N01266.

The proposed initiation doses provide lower exposures for all weight ranges than the 50 mg BID initiation dose that is used in adults. However, these doses were used in clinical trials in pediatric patients. As there was no apparent exposure-response with regard to adverse events in the pediatric trials, the clinical team and OCP determined that it would be appropriate to provide a dose range for the initiation dose that allowed for a minimum initiation dose that was the same as those used in the clinical trials and a maximum initiation dose that matched the exposures of the adult 50 mg BID initiation dose to allow prescribers the flexibility to initiate dosing without additional titration.

Based on PK simulations, OCP recommends the following initiation doses:
Patients 11 to < 20 kg: 0.5 to 1.25 mg/kg BID
Patients 20 to < 50 kg: 0.5 to 1.0 mg/kg BID
Patients ≥ 50 kg: 25 to 50 mg BID

Monotherapy Use of Briviact in Pediatric Pateints
As previously noted, a description in labeling of monotherapy dosing of Briviact was approved for all formulations in the POS indication in patients 16 years of age and older on September 14, 2017, based on extrapolation from its approved adjunctive dosing regimen. That analysis also supports the use of Briviact as monotherapy in the pediatric POS population. OCP cites the following rationale in their review:

Although there are some drugs that interact with BRV in the adjunctive setting (carbamazepine and phenytoin), none are clinically relevant to the extent that they require dose adjustment. Based on these considerations, and since adults have the same dosing for adjunctive therapy as for monotherapy, it is reasonable to apply the same pediatric dosing to monotherapy as is applied to adjunctive therapy in patients 4 years of age and older.

The approved labeling reflects the final agreed upon dosing with the applicant.

OCP Recommendation: OCP recommends approval of this supplement with the recommended dosing for pediatric patients aged 4 to 17 years for both monotherapy use and adjunctive use in the treatment of POS. OCP has recommended labeling changes to update pediatric dosing. I agree with the OCP recommendations.

5. Clinical Microbiology

No new data submitted or required.

6. Clinical/Statistical- Efficacy

Evidence for the effectiveness of Briviact in patients with POS aged 4 to <16 years is based on the prior demonstration of efficacy in adult patients with POS. Modeling and simulation was used to provide dosing recommendations for patients age 4 to <16 years that provide similar exposures to those found to be therapeutic in adult patients. Additionally, evidence for the effectiveness of monotherapy use of Briviact in POS patients age 4 to <16 years is based on the prior demonstration of efficacy when used as adjunctive therapy for the treatment of POS in adult patients and the expectation of similar exposures with monotherapy use of Briviact to adjunctive use of Briviact. Refer to Section 4 for a more detailed discussion of these analyses.

7. Safety

The safety data in this submission were reviewed by Dr. Steve Dinsmore, DNP clinical reviewer.

As described in Dr. Dinsmore's review, the primary sources of safety data were from Study N01263 and N01266, which were previously described in Section 4.

Dr. Dinsmore analyzed a pooled dataset from these two studies that focused on the patient population age 4 to <17 years of age to support pediatric extrapolation in this age group.

Table 1, copied from Dr. Dinsmore's review, shows the overall exposures and duration of treatment for the pooled dataset.

Table 1: Overall duration of exposure to brivaracetam by pediatric group

	BRV overall			
	POS summary group			All pediatric subjects N=219
	<4y N=16	≥4 to <16y N=149	Total POS N=168	
Number of subjects exposed, n (%)	16 (100)	149 (100)	168 (100)	219 (100)
Subject-years of exposure	36.9	249.7	290.0	399.5
Duration of exposure, n (%)				
≥1 month	14 (87.5)	143 (96.0)	160 (95.2)	211 (96.3)
≥3 months	13 (81.3)	125 (83.9)	140 (83.3)	185 (84.5)
≥6 months	13 (81.3)	116 (77.9)*	131 (78.0)*	166 (75.8)*
≥12 months	11 (68.8)	104 (69.8)*	117 (69.6)*	146 (66.7)
≥18 months	11 (68.8)	81 (54.4)	93 (55.4)	119 (54.3)
≥24 months	10 (62.5)	58 (38.9)	69 (41.1)	93 (42.5)
≥30 months	8 (50.0)	27 (18.1)	35 (20.8)	57 (26.0)
≥36 months	8 (50.0)	20 (13.4)	28 (16.7)	50 (22.8)
≥42 months	6 (37.5)	15 (10.1)	21 (12.5)	42 (19.2)
≥48 months	2 (12.5)	14 (9.4)	16 (9.5)	33 (15.1)
≥54 months	0	4 (2.7)	4 (2.4)	6 (2.7)
≥60 months	0	2 (1.3)	2 (1.2)	3 (1.4)

*Reviewer Confirmed from ADEXS and ADSL, study 1266 ADaM dataset, counts include 3 patients > 16 years of age with 0.175, 1.17 and 2.06 yrs of exposure.

There were 219 pediatric patients with epilepsy exposed to brivaracetam overall, with 166 patients exposed for at least 6 months, and 146 patients exposed for at least 1 year. There was adequate exposure to allow for an evaluation of safety in the pediatric population.

Overall, the safety profile of brivaracetam in pediatric patients with epilepsy age 4 to 17 years was found to be similar to the safety profile in adults and no new safety signals were identified.

7.1. Deaths

There were four deaths reported in the pediatric safety population. Three of these deaths had previously been reviewed in the initial NDA review and were not thought to be causally related to brivaracetam.

The new report of death occurred in a 6 year-old female with de Lange's syndrome who developed fatal septic shock and community-aquired pneumonia after 2.5 years of treatment with brivaracetam. This death was not assessed by the investigator, applicant, or Dr. Dinsmore as causally related to brivaracetam.

7.2. Nonfatal Serious Adverse Events

As noted in Dr. Dinsmore's review, 59 (26.9%) of the 219 pediatric subjects experienced a serious adverse event (SAE). The most common SAEs were convulsions (16 subjects) and status epilepticus (6 subjects) which commonly occur in this study population. Other SAEs that occurred in > 2 patients appeared to be unrelated to the drug treatment (e.g., pneumonia, gastroenteritis) or they are already included in approved labeling.

The incidence and character of the SAEs did not appear to be substantially different from what has been previously reported in the adult clinical trials. No new safety signals were identified.

7.3. Dropouts and Discontinuations

There were 26 (11.9%) patients who discontinued due to an AE. The most commonly reported TEAEs leading to discontinuation were aggression (3) and suicidal ideation (3). Two of the events of aggression were reviewed under the initial NDA submission. Psychiatric adverse events and suicidal ideation are already described in the Warnings section of approved labeling. No new safety signals were identified.

7.4. Common Adverse Events

As noted in Dr. Dinsmore's review, a total of 206 (94.1%) patients from the total pediatric population of 219 patients experienced a TEAE. Table 2, copied from Dr. Dinsmore's review, shows the most common TEAEs occurring across the pooled safety dataset. The types of TEAEs were generally similar to those reported in adult clinical trials. There were a large number of reports of infections (e.g., respiratory infections, otitis media, pharyngitis); however, these are commonly occurring events in a pediatric population and it is difficult to assess causality in the absence of a placebo control. Although incidence rates cannot be directly compared between the short-term controlled adult studies and the long-term open-label pediatric studies, there did not appear to be a substantial difference in rates of reported events to raise a concern for a new or unique safety signal in the pediatric population. Overall, no new safety signals were identified.

Table 2. Adverse events occurring in >2% of the pediatric population

PT (all Pediatric) N= 219	# Patients	% patients	# events	PT (all Pediatric)	# Patients	% patients	# events
Nasopharyngitis	60	27.4	129	Oropharyngeal pain	10	4.6	12
Pyrexia	50	22.8	123	Rhinitis allergic	10	4.6	11
Convulsion	44	20.1	80	Varicella	10	4.6	11
Vomiting	43	19.6	70	Laryngitis	9	4.1	14
Pharyngitis	42	19.2	68	Nausea	9	4.1	11
Headache	36	16.4	98	Gamma-glutamyltransferase increased	9	4.1	9
Diarrhoea	33	15.1	49	Suicidal ideation	9	4.1	9
Upper respiratory tract infection	29	13.2	52	Toothache	8	3.7	28
Pharyngotonsillitis	27	12.3	83	Sinusitis	8	3.7	14
Gastroenteritis	26	11.9	38	Rash	8	3.7	13
Cough	26	11.9	37	Conjunctivitis	8	3.7	10
Somnolence	26	11.9	35	Gastrooesophageal reflux disease	8	3.7	10
Decreased appetite	26	11.9	34	Respiratory tract infection	7	3.2	38
Irritability	26	11.9	34	Acute tonsillitis	7	3.2	12
Rhinitis	21	9.6	46	Dehydration	7	3.2	9
Bronchitis	19	8.7	46	Psychomotor hyperactivity	7	3.2	8
Influenza	18	8.2	19	Laceration	6	2.7	11
Fall	17	7.8	21	Abnormal behaviour	6	2.7	8
Abdominal pain	15	6.8	26	Epistaxis	6	2.7	8
Ear infection	14	6.4	17	Otitis media acute	6	2.7	8
Fatigue	13	5.9	19	Pharyngitis bacterial	6	2.7	7
Constipation	13	5.9	18	Ear pain	6	2.7	6
Insomnia	13	5.9	16	Dysmenorrhoea	5	2.3	29
Weight decreased	13	5.9	15	Rhinorrhoea	5	2.3	9
Abdominal pain upper	13	5.9	14	Head injury	5	2.3	8
Otitis media	12	5.5	38	Asthenia	5	2.3	7
Pneumonia	12	5.5	24	Contusion	5	2.3	7
Aggression	12	5.5	14	Status epilepticus	5	2.3	7
Dizziness	11	5.0	21	Blood triglycerides increased	5	2.3	6
Viral infection	11	5.0	17	Creatinine renal clearance decreased	5	2.3	5
Pharyngitis streptococcal	11	5.0	13	Dental caries	5	2.3	5
Urinary tract infection	10	4.6	15	Tonsillitis	5	2.3	5
				Viral pharyngitis	5	2.3	5

* Reviewer Pool Dataset, see **Error! Reference source not found.**

7.5. Adverse Events of Interest

Psychiatric adverse events have previously been identified as a safety concern with brivaracetam and are listed as a Warning in the prescribing information. Dr. Dinsmore did a focused review of psychiatric adverse events to determine if there was a new or different

signal in the pediatric population. The character of psychiatric adverse events appeared to be comparable to those reported in the adult population.

7.6. Laboratory Findings/Vitals/ECG

Although there were a few isolated events of laboratory abnormalities noted, there were no clinically concerning trends in laboratory assessments, vital signs, weight, or ECGs identified by Dr. Dinsmore.

7.7. Safety by Age Group

Dr. Dinsmore did not identify any differences in the incidence or quality of TEAEs across the age groups.

7.8. Postmarket Experience

The applicant conducted a search of its global postmarket safety database using a data lock of October 14, 2016. The search identified 26 reports containing 82 adverse events in pediatric patients age 4 to < 16 years. Dr. Dinsmore reviewed these reports and found that the majority reported off-label use of Briviact. Of the adverse events that were captured, the majority of events were consistent with those seen in the adult patient population.

Dr. Dinsmore also did a general search of FAERS and Empirica Signal search and did not identify any new safety signals.

Clinical recommendation: Dr. Dinsmore did not identify any new or unique safety signals for brivaracetam in the pediatric population age 4 to 17 years. He recommends approval of this supplement and I agree with his recommendation.

8. Advisory Committee Meeting

None required.

9. Pediatrics

The submission was discussed with the Pediatric Review Committee.

The following PREA PMR has been fulfilled by the pediatric extrapolation submission for patients with partial onset seizures age 4 years to 17 years:

3042-1: A pharmacokinetic analysis to determine a dosing regimen in children from 4 years to less than 16 years of age that provides drug exposure that is similar to the exposure that is effective in adult patients with partial onset seizures. This analysis will require pharmacokinetic data from studies of both adult and pediatric patients. These studies have already been performed.

The following PREA PMR has been partially addressed by the pediatric extrapolation submission for patients with partial onset seizures age 4 years to 17 years:

3042-4: Long-term safety study of brivaracetam in the adjunctive treatment of partial onset seizures in children from 1 month to less than 16 years of age. Routine safety measures should be monitored. Behavioral and cognitive endpoints should be included. A total of at least 200 patients must be enrolled. Subjects should be balanced among age cohorts.

This PMR will be released and reissued as a new PMR (language in following paragraph) to cover the aspects of the PMR that remain unfulfilled; namely, the adjunctive and monotherapy use of Briviact for the treatment of partial onset seizures in the age group 1 month to < 4 years.

Long-term safety study of brivaracetam in the treatment of partial onset seizures in children from 1 month to less than 4 years of age. Routine safety measures should be monitored. Behavioral and cognitive endpoints should be included.

10. Labeling

The Division of Pediatrics and Maternal Health, Division of Medication Error Prevention and Analysis, and the Office of Prescription Drug Promotion provided consultations on labeling and their recommendations were incorporated into the labeling revisions. Please see final label and discussions in the above review.

11. Recommendations/Risk Benefit Assessment

The sponsor has provided substantial evidence of effectiveness for the monotherapy and adjunctive use of Briviact tablets and oral solution in pediatric patients aged 4 to < 17 years with POS based on the prior findings of efficacy and safety of Briviact in the adult population and pharmacokinetic modeling for dosing that provides similar exposures to those found to be therapeutic in adult patients. There are no new safety concerns identified with the use of Briviact in this population. There are no outstanding unresolved issues.

The PREA PMR 3042-1 for the oral formulations of Briviact under NDA 205836 and 205838 has been partially fulfilled for patients age 4 years of age and older. Additional safety information will be required for the IV formulation under NDA 205837. Additionally, PREA PMR 3042-4 is partially addressed for ages 4 years and older. PMR 3042-4 will be released and a new PMR will be reissued to cover the PMR requirements for long-term safety for partial onset seizures in the age group 1 month to < 4 years.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of Briviact for the treatment of partial onset seizures in patients age 4 to < 17 years.

I agree with the review team that this supplemental application should be approved.

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

/s/

TERESA J BURACCHIO
05/10/2018

WILLIAM H Dunn
05/10/2018