Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	October 4, 2022
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Product Name:	Briviact (brivaracetam)
Pediatric Labeling Approval Date:	May 10, 2018; August 27, 2021
Application Type/Number:	NDA 205836 (tablet), NDA 205837 (injection), NDA 205838 (oral solution)
Applicant:	UCB, Inc
TTT #:	2022-1172

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Briviact (brivaracetam) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV)-I conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with brivaracetam in pediatric patients.

The FDA approved brivaracetam on February 18, 2016, for the adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy; since that time, it has received approval for monotherapy dosing for the treatment of partial-onset seizures. The approved pediatric labeling is for the treatment of partial-onset seizures in patients 1 month of age and older. This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on May 10, 2018, and August 27, 2021.

We reviewed all FAERS U.S. serious cases with brivaracetam in the pediatric population (ages 0 to <17 years) during the period of February 18, 2016, through August 31, 2022. Our evaluation identified one case describing alopecia totalis associated with brivaracetam use; however, there is insufficient evidence to support a new signal at this time. We did not identify any additional new safety signals, increased severity or frequency of any labeled adverse events, or deaths directly associated with brivaracetam.

DPV-I did not identify any new pediatric safety concerns for brivaracetam at this time. DPV-I recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of brivaracetam.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for brivaracetam in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV)-I conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with brivaracetam in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Briviact (brivaracetam) oral tablet, oral solution, and injection formulations were initially approved by the FDA on February 18, 2016, for the adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.[1] On September 14, 2017, brivaracetam received approval from the FDA to include a description in the labeling of monotherapy dosing for all formulations of brivaracetam.[2]

On May 10, 2018, the FDA approved the expansion of the use of brivaracetam tablets and oral solution for the treatment of partial-onset seizures to include patients 4 years to less than 16 years of age based on the prior findings of efficacy and safety of brivaracetam in the adult population and pharmacokinetic modeling for dosing that provides similar exposures to those found to be therapeutic in adult patients.[3]

On August 27, 2021, the FDA approved the expansion of the use of brivaracetam tablets and oral solution for the treatment of partial-onset seizures to include patients 1 month to less than 4 years of age, and the expansion of the use of brivaracetam injection to include patients ages 1 month to less than 16 years of age based on extrapolation of efficacy data from adults, the Applicant's long-term safety data for the expanded pediatric population, and pharmacokinetics modeling for dosing that provides similar exposures to those found to be therapeutic in adult patients.[4,5]

Briviact (brivaracetam) is currently indicated for the treatment of partial-onset seizures in patients 1 month of age and older.[6] Briviact is supplied as 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg oral tablets; 10 mg/ml oral solution; and 50 mg/5ml injection for intravenous use.

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on May 10, 2018, and August 27, 2021. DPV-I has not previously presented brivaracetam to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

A summary of the safety information from the HIGHLIGHTS OF PRESCRIBING INFORMATION section and Pediatric Use subsection of the brivaracetam product labeling is reproduced below.[6]

---------- CONTRAINDICATIONS ----------
Hypersensitivity to brivaracetam or any of the inactive ingredients in BRIVIACT. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and ideation. (5.1)
- Neurological Adverse Reactions: Monitor for somnolence and fatigue, and advise patients not to drive or operate machinery until they have gained sufficient experience on BRIVIACT. (5.2)
- Psychiatric Adverse Reactions: Behavioral reactions including psychotic symptoms, irritability, depression, aggressive behavior, and anxiety; monitor patients for symptoms. (5.3)
- Hypersensitivity Bronchospasm and Angioedema: Advise patients to seek immediate medical care. Discontinue and do not restart BRIVIACT if hypersensitivity occurs. (5.4)
- Withdrawal of Antiepileptic Drugs: BRIVIACT should be gradually withdrawn. (5.5)

----------ADVERSE REACTIONS----------

Adults Most common adverse reactions (at least 5% for BRIVIACT and at least 2% more frequently than placebo) are somnolence/sedation, dizziness, fatigue, and nausea/vomiting. (6.1)

Pediatric Patients Most common adverse reactions are similar to those seen in adult patients. (6.1)

8 USE IN SPECIFIC POPULATIONS

8.4 *Pediatric Use*

Safety and effectiveness of BRIVIACT have been established in pediatric patients 1 month to less than 16 years of age. Use of BRIVIACT in these age groups is supported by evidence from adequate and well-controlled studies of BRIVIACT in adults with partial-onset seizures, pharmacokinetic data from adult and pediatric patients, and safety data in pediatric patients 2 months to less than 16 years of age *[see Dosage and Administration (2.1), Warnings and Precautions (5.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].*

Safety and effectiveness in pediatric patients below the age of 1 month have not been established.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy[*]

Date of search	September 1, 2022
Time period of search	February 18, 2016[†] - August 31, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product active ingredient: Brivaracetam
MedDRA search terms (Version 25.0)	All PT terms

Table 1. FAERS Search Strategy*
* See Appendix A for a description of the FAERS database. † U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from February 18, 2016, through August 31, 2022, with brivaracetam.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 18, 2016 through August 31, 2022 With Brivaracetam

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	1,432 (610)	1,295 (485)	97 (30)
Pediatrics (0 - <17 years)	198 (54)	**173 (32)‡**	**19 (1)‡**

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1. One additional report of pediatric death was identified among U.S. reports not reporting an age. This report is reflected in the counts of pediatric reports.

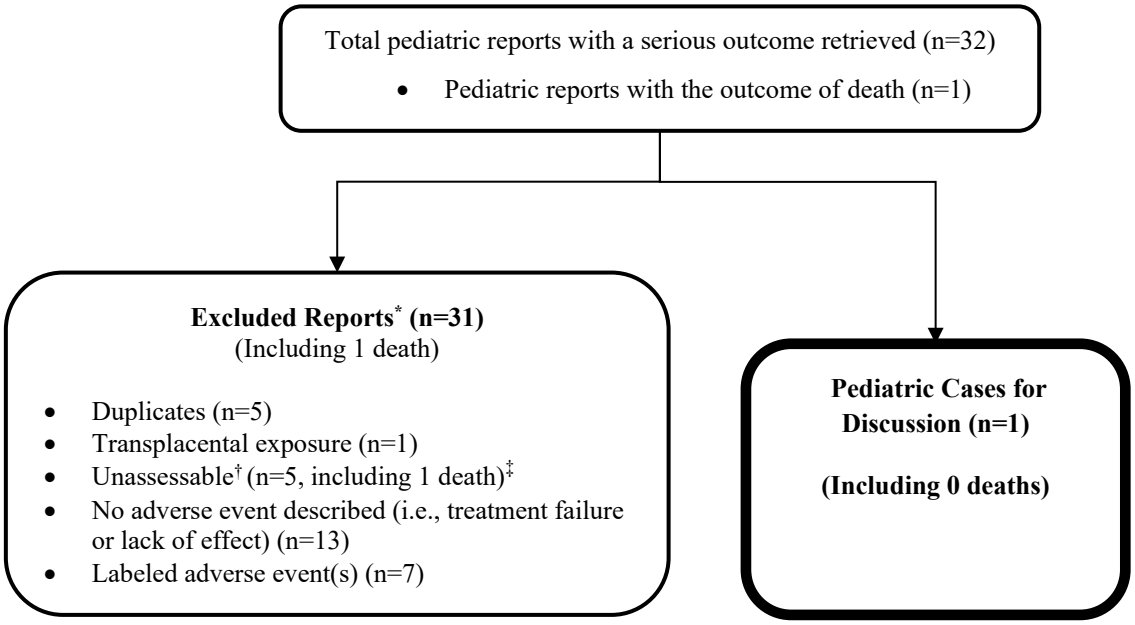
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 32 U.S. serious pediatric reports from February 18, 2016, through August 31, 2022.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as duplicate reports, unassessable reports, no adverse event described, labeled adverse event without new features.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Brivaracetam



* DPV 1 reviewed these reports, but they were excluded from further discussion for the reasons listed above

† Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the report cannot be supplemented or verified.

‡ This includes one report of death in a "pediatric male" that contained insufficient information for causality assessment.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=1)

We identified one serious FAERS case with brivaracetam in the U.S. pediatric population reporting a non-fatal serious outcome. Appendix B contains a line listing of this case. The case is summarized below:

FAERS Case#16931385; MCN: US-UCBSA-2019043369:

A 16-year-old male patient was treated with oral brivaracetam 100 mg twice daily for epilepsy and generalized tonic-clonic seizures. Medical history included attention deficit/hyperactivity disorder (ADHD), celiac disease and metabolic disorder. Concomitant medication included lamotrigine (dose and frequency was not reported). Approximately two months after initiation of brivaracetam, the patient experienced alopecia totalis, which was described as "significant hair loss on top of scalp and diffuse hair on rest of the scalp" that worsen with time and "it was on the entire head." Laboratory tests (not otherwise specified) were completed which were normal, including "full blood count," except for serum iron (26 mcg/dl; normal range 30-130), iron saturation (8%; normal range 15-45). The patient was given iron supplement. Brivaracetam was continued and alopecia totalis was not resolved.

Reviewer comments: This case described temporal association between brivaracetam exposure and onset of alopecia totalis. Alopecia totalis is a severe form of alopecia areata. It is a chronic, autoimmune disorder involving complete hair loss of the scalp, often accompanied by hair loss of the eyebrows and eyelashes.[7] To our knowledge, no studies link brivaracetam to autoimmune reactions. The narrative describes some degree of iron deficiency in the patient. Iron deficiency has been linked to hair loss; however, data linking iron deficiency to alopecia areata is equivocal.[8,9] A robust causality assessment is limited by missing information and concomitant use of lamotrigine, a medication labeled for alopecia in the ADVERSE REACTIONS section.[10] The case also did not report when lamotrigine was initiated with respect to the start of alopecia totalis. An exploratory search of the FAERS database identified no additional cases of alopecia totalis with brivaracetam. There is insufficient evidence to support a signal of alopecia totalis with brivaracetam at this time.

4 DISCUSSION

We reviewed all FAERS U.S. serious cases with brivaracetam in the pediatric population (ages 0 to <17 years) during the period of February 18, 2016, through August 31, 2022. Our evaluation identified one case describing alopecia totalis with brivaracetam; however, there is insufficient evidence to support a new signal at this time.

5 CONCLUSION

DPV-I did not identify any new pediatric safety concerns for brivaracetam at this time.

6 RECOMMENDATION

DPV-I recommends no regulatory action at this time, and will continue to monitor all adverse events associated with the use of brivaracetam.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	17-OCT-2019	16931385	2	US-UCBSA-2019043369	15-DAY	16	Male	USA	Other

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUPRAT N SAELY
10/04/2022 11:47:05 AM

IVONE E KIM
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CARMEN CHENG
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CINDY M KORTEPETER
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