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

Pediatric Postmarketing Pharmacovigilance Review

Date:	December 21, 2017
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Product Name(s):	Banzel™ (rufinamide)
Pediatric Labeling Approval Date:	2/12/2015
Application Type/Number:	NDA #21911 (oral tablets) and #201367 (oral suspension)
Applicant/Sponsor:	Eisai
OSE RCM #:	2017-1002

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for Banzel (rufinamide) in pediatric patients.

FDA first approved rufinamide oral tablets on 11/14/2008 and subsequently approved rufinamide oral suspension on 3/3/2011 for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in pediatric patients 4 years and older and in adults. FDA approved rufinamide (oral tablets and oral suspension) on 2/12/2015 for adjunctive treatment of seizures associated with LGS in pediatric patients 1 year of age and older.

We identified 16 U.S. pediatric FAERS cases with rufinamide reporting serious outcomes, including two fatalities, covering the period 2/12/2014 to 5/19/2017. Our review of the adverse events reported in the 16 FAERS cases with rufinamide did not identify any new safety concerns. The majority of reported adverse events were consistent with the known risks described in the labeling and no apparent increased severity was observed in these cases. Some labeled events were related to skin events, gastrointestinal disorders, specific seizure types, and central nervous system effects. These adverse events are adequately described in the labeling.

We identified three foreign pediatric FAERS cases reporting three unlabeled adverse events, one was also reported in the literature. The three adverse events include hyperammonemia (1), rhabdomyolysis (1), and agranulocytosis (1). Two of the three cases reported alternative causes for the adverse events, i.e., overdose and underlying disease. The first case reported hyperammonemia coincident with an accidental overdose of prescribed medications (including valproate), which resolved upon temporary suspension of the three drugs; all three medications were restarted at the recommended doses, without reoccurrence of hyperammonemia. The second case reported rhabdomyolysis in a patient with LGS and carnitine deficiency. The occurrence of multiple tonic seizures, a tonic status epilepticus, or an unwitnessed tonic-clonic seizure in LGS could explain the rigidity and rhabdomyolysis, and carnitine deficiency myopathy exacerbated by febrile illness could also explain the rhabdomyolysis. The third case reported agranulocytosis that occurred 17 days after adding rufinamide to existing valproate and lamotrigine therapy; agranulocytosis resolved after discontinuing rufinamide. We did not identify any additional FAERS cases of agranulocytosis in all ages since its initial approval in 2008. We will continue postmarketing surveillance of all adverse events associated with the use of rufinamide including agranulocytosis in all patient populations.

1 INTRODUCTION

Banzel™ (rufinamide) U.S. approval and available dosage forms are as follows:

- NDA#21-911 approved on 11/14/2008: oral film coated tablet (200 mg and 400 mg)
- NDA#201-367 approved on 3/3/2011: oral suspension (40mg/mL)

1.1 PEDIATRIC REGULATORY HISTORY

1.1.1 Rufinamide Pediatric Labeling Changes[1]

FDA first approved rufinamide on 11/14/2008 for adjunctive treatment of Lennox-Gastaut Syndrome (LGS) in pediatric patients age ≥4 years and adults. The effectiveness of rufinamide as adjunctive treatment for seizures associated with LGS was established in a single, pivotal, multicenter, double-blind, placebo-controlled, randomized, parallel-group study. The current pediatric labeling change, in pediatric patients age ≥1 year, occurred on 2/12/2015. The approval of rufinamide in pediatric patients ages ≥1 to <4 years was based upon a bridging pharmacokinetic and safety study. Because the course of LGS is physiologically similar and treatment with rufinamide are sufficiently similar in the ≥4-year-old pediatric age group to the <4-year-old pediatric age group, the effectiveness demonstrated in the original trial in the pediatric patients age >4 years was extrapolated to the younger patients. Consequently, the Division of Neurology Products (DNP) approved the extension of the rufinamide indication for treatment of seizures associated with LGS in pediatric patients ages ≥1 to <4 years.

No new safety issues were observed in the PK and safety study in pediatric patients ages ≥1 to <4 years and adverse reactions were similar to those observed in adults and pediatric patients 4 years and older. Adverse reactions that occurred in the rufinamide-treated patients included vomiting, somnolence, bronchitis, constipation, cough, decreased appetite, rash, otitis media, pneumonia, decreased weight, gastroenteritis, nasal congestion, and pneumonia aspiration.

Safety and effectiveness in pediatric patients <1 year has not been established.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The rufinamide labeling dated 6/25/15 contains the following safety information: [2]

CONTRAINDICATIONS

- Banzel is contraindicated in patients with Familial Short QT syndrome

WARNINGS AND PRECAUTIONS

- Suicidal Behavior and Ideation
- Central Nervous System (CNS) Reactions
- QT Shortening
- Multi-organ Hypersensitivity/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Withdraw of AEDs
- Status Epilepticus

- Estimates of the incidence of treatment emergent status epilepticus among patients treated with BANZEL are difficult because standard definitions were not employed. In a controlled Lennox-Gastaut Syndrome trial, 3 of 74 (4.1%) BANZEL-treated patients had episodes that could be described as status epilepticus in the BANZEL-treated patients compared with none of the 64 patients in the placebo-treated patients. In all controlled trials that included patients with different epilepsies, 11 of 1240 (0.9%) BANZEL-treated patients had episodes that could be described as status epilepticus compared with none of 635 patients in the placebo-treated patients.

- Leukopenia
  - BANZEL has been shown to reduce white cell count. Leukopenia (white cell count < $3X10^9$ L) was more commonly observed in BANZEL-treated patients 43 of 1171 (3.7%) than placebo-treated patients, 7 of 579 (1.2%) in all controlled trials.

ADVERSE REACTIONS

- Most common adverse reactions (≥ 10% and greater than placebo) were headache, dizziness, fatigue, somnolence, and nausea.

USE IN SPECIFIC POPULATIONS

- Pediatric Use
  - Safety and effectiveness have been established in pediatric patients 1 to 17 years of age. The effectiveness of BANZEL in pediatric patients 4 years of age and older was based upon an adequate and well-controlled trial of BANZEL that included both adults and pediatric patients, 4 years of age and older, with Lennox Gastaut Syndrome. The effectiveness in patients 1 to less than 4 years was based upon a bridging pharmacokinetic and safety study [see Dosage and Administration (2.1), Adverse Reactions (6.1), and Clinical Studies (14)]. The pharmacokinetics of rufinamide in the pediatric patients, ages 1 to less than 4 years of age is similar to children older than 4 years of age and adults [see Clinical Pharmacology (12.3)].

CLINICAL PHARMACOLOGY

Special Populations

Age

- Pediatrics Based on a population analysis which included a total of 115 patients, including 85 pediatric patients (24 patients ages 1 to 3 years, 40 patients ages 4 to 11 years, and 21 patients ages 12 to 17 years), the pharmacokinetics of rufinamide was similar across all age groups.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategies described in Table 1. See Appendix A for a description of the FAERS database.

Table 1. FAERS Search Strategy	
Product Names (s)	Banzel (product name) and rufinamide (active ingredient)
Search Type	FBIS – Profile Report (product manufacturer reporting summary) query
Search #1	
Date of Search	5/19/2017
Time Period of Search	2/12/2014* – 5/19/2017
Search Parameters	All ages, all outcome, worldwide (MedDRA PTs v 20.0)
Search #2	
Date of Search	9/5/2017
Time Period of Search	All reports through 9/5/2017
MedDRA term	Agranulocytosis (PT)

* *A year prior to a comprehensive OND review, including rufinamide safety information from FAERS spontaneous data.*

We identified all U.S. pediatric (ages newborn to <17 years) FAERS reports with a serious outcome covering the period 2/12/2014 to 5/19/2017. Serious outcomes per the regulatory definition (CFR 314.80) include death, life-threatening event, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. We examined the drug-event combinations (DECs) during this period for serious and unlabeled adverse events with rufinamide. A DEC is a drug and adverse event combination reported in at least one case in the database. Cases may have more than one reported DEC.

We also reviewed all designated medical events (DMEs) in U.S. pediatric FAERS cases during this period to capture adverse events that are considered rare, serious, and associated with a high drug-attributable risk. The Office of Surveillance and Epidemiology (OSE) created the DME list for working purposes; it has no regulatory significance. See Appendix B for a list of OSE's DMEs. Furthermore, we used Empirica Signal to perform data mining analysis on all reported DECs for rufinamide since product approval (2008) for all pediatric and adult FAERS reports. Data mining analysis identifies patterns (i.e., disproportionate ratios) of an association or an unexpected occurrence (i.e., "potential signals") in large databases (e.g., FAERS). Data mining complements our overall signal detection approaches in routine assessment of spontaneous adverse event report data. Data mining scores do not, by themselves, demonstrate causal associations; rather, they serve as a signal for further investigation. See Appendix A for a description of data mining of FAERS data using Empirica Signal.

For this review, we focused on FAERS U.S. cases reporting any serious DEC and FAERS foreign cases reporting unlabeled DEC's in the pediatric population from 2/12/2014 to 5/19/2017.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2. Total Adult and Pediatric FAERS Reports* for Rufinamide Received from 2/12/2014 to 5/19/2017

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	76 (38)	30 (10)	0 (0)
Pediatrics (0 - <17 years)	74 (27)	46 (18)	2 (2)

* *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, and other serious important medical events*

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 18 U.S. pediatric reports with a serious outcome covering the period 2/12/2014 to 5/19/2017 (See above Table 2). After accounting for duplicate reports, 16 cases were included in our case series, including 2 deaths.

2.2.3 Characteristics of Pediatric Case Series

Table 3 summarizes the 16 FAERS cases in U.S. pediatric patients with rufinamide reporting a serious outcome received by FDA from 2/12/2014 to 5/19/2017.

Appendix C has a line listing of the 16 cases in our pediatric case series.

Table 3. Characteristics of the Pediatric Case Series with Rufinamide (N=16)

Age	0 - < 1 year (off-label)	1
	≥1 - <5 years	5
	6- <12 years	6
	12- < 17 years	4
Sex	Male	10
	Female	5
	Unknown	1
Country	United States	16
Reported Reason for Use	Lennox-Gastaut	7
	Seizure/ Epilepsy	2
	Status Epilepticus	3
	Unspecified	3
	Malignant migrating partial seizure	1

Table 3. Characteristics of the Pediatric Case Series with Rufinamide (N=16)		
Serious Outcome*	Death	2
	Life-threatening	0
	Hospitalized	3
	Disability	0
	Congenital anomaly	0
	Required Intervention	0
	Other serious	11

* *For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.*

2.3 SUMMARY OF U.S. FATAL PEDIATRIC ADVERSE EVENT CASES (N=2)

We identified two FAERS cases reporting death as an outcome. Both cases are unlikely related to rufinamide use. Below is a summary of the two cases:

FAERS #11138725/MFR #PHHY2015US062564/US/2015
This case describes a 9-week-old male with a history of malignant migrating partial seizure occasionally associated with apnea and respiratory infections receiving pyridoxine, pyridoxal-5-phosphate, and folinic acid. On an unknown date, he received levetiracetam, topiramate, lacosamide, rufinamide, clonazepam, phenobarbital, and unspecified anesthetics for the treatment of epilepsy. Despite multiple therapies, his seizures persisted. On an unknown date, he started on a ketogenic diet along with vagal nerve stimulation, phenytoin, primidone and felbamate. There was 50% reduction in seizure. Anesthetics were weaned off and he developed a febrile infection (site unknown) and his seizure activity briefly increased. At age 13 months, he died of a respiratory infection.

Reviewer's comment:
This case described a 9-week-old male with a history of migrating partial seizures occasionally associated with apnea and respiratory infections, who died at 13 months of a respiratory infection. It is likely that levetiracetam, topiramate, lacosamide, rufinamide, clonazepam, and phenobarbital were discontinued when therapy was switched to a ketogenic diet and phenytoin, primidone and felbamate therapy. His respiratory infection is unlikely related to rufinamide use prior to his death.

FAERS #13232365/MFR #US-EISAI-EC-2017-024873/US/2017
This case describes a 16-year-old female with LGS receiving rufinamide for an unknown period and was found unresponsive in her bed. Her seizures were well controlled at the time of her death. Autopsy findings were compatible with the clinical history of a seizure disorder, and no anatomic cause for sudden death was identified. The cause of death was attributed to sudden unexpected death in epilepsy (SUDEP).

2.4 SUMMARY OF U.S. NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=14)

We identified 14 U.S. non-fatal pediatric FAERS cases with 50 DECs with rufinamide reporting serious outcomes. There were more males than females using rufinamide primarily to control seizures associated with LGS. Rufinamide is indicated for LGS and the primary indication in our case series was LGS. The predominance of males is likely because LGS affects males more than females. The current product labeling includes treatment for pediatric patients >1 year of age and older. In our case series, the pediatric ages ranged from 9 weeks to <17 years. One case reported use in a patient <1 years-old, which is off-label use. This single case involving a nine-week-old is described above in section 2.3.

The majority of the reported DECs were consistent with the known risks described in the labeling. The most frequently reported DECs in ≥3 cases included the following:

- Coordination abnormalities; gait disturbance
- Constipation
- Appetite disorder
- Fatigue
- Pneumonia; respiratory infection
- Rash

We evaluated status epilepticus (SE) cases because the current rufinamide labeling in the WARNINGS AND PRECAUTIONS section describes one specific type of seizure, SE, in patients with LGS. LGS is a type of epilepsy with multiple types of refractory seizures including SE. We identified three FAERS cases of SE with rufinamide. These three cases involved pediatric patients treated for LGS (n=2) and epilepsy (n=1) who received less than the maximum recommended dose, i.e., < 3200 mg daily, and experienced SE. All three patients were enrolled in an ongoing sponsor conducted postmarketing study #E2080-IN001T (NCT02175173) of long-term administration of rufinamide in patients, including pediatrics, which started enrolling on 6/13/2013 and is expected to end in 4/2018.[3] The purpose of the study includes characterizing unknown adverse events, efficacy of long-term administration and risk factors, and determining the incidence of rufinamide adverse events including SE, skin disorders, and central nervous system-related adverse events, which are labeled.

Because a decrease in body weight may affect pediatric growth and development, we evaluated pediatric reports of appetite disorder. We identified three cases reporting appetite disorder in pediatric patients ages 3, 8, and 14 years. These three cases reported "lack of appetite" in the context of other non-specific adverse events and did not provide any additional information to assess weight changes.

An evaluation of the U.S. serious unlabeled DECs revealed either poor documentation including the lack of case elements needed for causality assessment, e.g., temporal association and dechallenge information, or reported alternative etiologies.

2.5 FOREIGN REPORTS OF SERIOUS UNLABELED ADVERSE EVENTS (N=3)

We reviewed the foreign pediatric reports during this period and identified three serious

unlabeled DECs in the FAERS foreign pediatric reports. These events include one case each of hyperammonemia, rhabdomyolysis, and agranulocytosis. These three cases are described below.

2.5.1 Hyperammonemia (N=1)

FAERS #11875483/MFR #PHHY2015IT168927/Italy/2015
This case describes a 4-year-old female patient with a history of herpes simplex induced encephalitis at the age of 9-months old. The patient received valproate sodium and oxcarbazepine for the treatment of epilepsy at unknown doses for 2 and 3 years, respectively. The patient started on rufinamide tablets at an unknown dose for the treatment of epilepsy. On day 153, she had an accidental overdose (she was administered valproic acid, rufinamide, and oxcarbazepine at a dose of 500 mg, 600 mg, and 900 mg, respectively) and she experienced somnolence and hyperammonemia. The patient was hospitalized on an unknown date for the events. Therapy with the suspect drugs was suspended on the same day of admission with an improvement in her condition. On day 154, her ammonia level increased to 154 mcg/dL (at 00:09) and 66 mcg/dL (at 10:48) (normal range was 19 - 87 mcg/dL). During the hospitalization, the patient's clinical condition improved, and the suspect drugs were re-administered at her recommended dosages without reoccurrence of any adverse event (unknown dates and doses). On day 155, she recovered and was discharged.

Reviewer's comment:
Rufinamide was the last drug added to a regimen of long-term use of valproic acid and oxcarbazepine and temporal (154 days) to the onset of hyperammonemia. However, she received increased doses (overdoses) of all three medications, including valproate, prior to the onset of the hyperammonemia. Hyperammonemia is a well-known adverse event associated with valproic acid. All three drugs were discontinued and the patient improved, and all medications were restarted without reoccurrence of hyperammonemia. Valproate overdosing was more likely associated with her hyperammonemia.

2.5.2 Rhabdomyolysis (N=1)

FAERS#10970447/MFR #JP-EISAI Medical Research-EC-005430/2015/Japan
This case describes a 3-year-old male who was started on rufinamide for the treatment of LGS. His rufinamide starting dose was 100 mg, which increased to 200 mg on the third day. On day four, he experienced continuous strong muscle tightness with a high fever of 42 degrees Celsius, and laboratory findings showed creatine kinase increased to 4000 U/L. He was diagnosed with rhabdomyolysis and treated with dantrolene, fluid replacement, and cooling methods. Rufinamide was discontinued on the same day. The next day his symptoms improved. Concomitant medications included phenobarbital, zonisamide, valproate, lamotrigine, trihexyphenidyl, L-carnitine, cercine, carbocisteine, and budesonide (dosage and duration was not provided for any of the medications). Medical history included asthma, bronchitis, carnitine deficiency, gastrooesophageal reflux, and myotonia.

Reviewer's Comments
Rufinamide was the last drug added to his anticonvulsant regimen and the only reported drug discontinued after event onset. This case suggests a possible association with rufinamide use

because of a temporal association (4 days) and a positive dechallenge. His fever was suspected in association with hypertonia, which was treated concurrently. LGS is characterized by frequent seizures of multiple types. Although the case did not report seizure activity temporal to the onset of rhabdomyolysis, multiple tonic seizures, a tonic status epilepticus, or an unwitnessed tonic-clonic seizure in LGS could explain the rigidity and rhabdomyolysis. Carnitine deficiency related myopathy may also result in elevated creatine kinase when exacerbated by certain factors, e.g., febrile illness. This patient was enrolled in an ongoing sponsor conducted postmarketing study #E2080-IN001T (NCT02175173).[3]

2.5.3 Agranulocytosis (N=1)

FAERS#11366042/ MFR #EISAI-E2080-00670-SOL-JP/Japan/2015 (literature)[4]
This case describes a 10-year-old male with a history of herpes encephalitis at the age of 1 year who developed LGS. Because of difficulties in controlling tonic seizures, rufinamide (200 mg/day) was added to valproate (900 mg/day), lamotrigine (100 mg/day), and clonazepam (0.6 mg/day) (duration was not provided). Laboratory studies before starting rufinamide revealed a white blood cell (WBC) count of 6900 cells/mm^3 and a neutrophil count of 3200 cells/mm^3 with normal differential. On day 17 his dose of rufinamide was increased to 400 mg and he developed cheek rash and high fever. The rash gradually spread to his trunk and limbs, with the lesions fusing together. The high fever of 40 degrees Celsius lasted for three days. Rufinamide was discontinued on the third day of the rash. He was admitted to the hospital the next day. He had a low-grade fever of 37 degrees Celsius. The rash covered his face, trunk, and limbs. It consisted of regular, round- shaped, characteristic target lesions less than 1 cm in diameter, consistent with erythema multiform (EM). There were no other abnormalities, no mucosal membrane lesions, and no lymphadenoma or hepatosplenomegaly.

Laboratory results revealed low WBC count (500 cells/mm^3), and he was diagnosed with agranulocytosis. Blood examination revealed increased C-reactive protein (1.3 mg/dl) and lactate dehydrogenase (606 IU/L) without any evidence of multiple organ involvement. Liver enzymes and coagulation parameters were within the normal range. Tests for Epstein-Barr virus, parvovirus B19, measles virus, rubella virus, herpes simplex virus, and mycoplasma were all negative. Bone marrow aspiration revealed normal cellular marrow with complete absence of mature myeloid series (i.e., almost complete absence of segmented and band neutrophils with normal metamyelocytes or more immature myeloid cells), without any signs of malignancy or hemophagocytic syndrome. Erythropoiesis and thrombopoiesis were not affected. A drug patch test (DPT) for rufinamide was negative.

His symptoms started to improve on day three following rufinamide discontinuation. He was not treated with granulocyte colony-stimulating factor (G-CSF) or any other treatment, and his fever did not recur after discontinuing rufinamide. The rash did not worsen thereafter and resolved spontaneously. Mature neutrophils appeared in blood on the 5th day. On the 7th day, his neutrophils reached a count of 990 cells/mm^3, and on the 9th day the counts increased to the normal range. Eventually his symptoms resolved after rufinamide was discontinued.

Reviewer's comment:
This foreign literature case suggests a possible causal association for rufinamide induced EM (labeled for SJS) and agranulocytosis because of a temporal relationship (day 17) to the onset of the event and positive dechallenge following rufinamide discontinuation. Further, his baseline WBC values were normal before adding rufinamide to existing therapy with other antiepileptic drugs (AEDs), including valproate and lamotrigine (both labeled for agranulocytosis). Rufinamide was the only drug discontinued and the patient recovered. Rufinamide is labeled for leukopenia in the WARNINGS AND PRECATIONS section. For completeness, we performed a search of FAERS for additional agranulocytosis cases. We did not identify any additional agranulocytosis cases. We will continue to monitor for cases of agranulocytosis

3 DISCUSSION

We reviewed 16 FAERS cases with rufinamide in the U.S. pediatric population (ages newborn to <17 years) covering the period 2/12/2014 to 5/19/2017. Our analysis revealed primarily rufinamide users at recommended ages ≥1 year (n=15) for the treatment of LGS and "epilepsy," which the latter may or may not be LGS (n=13). One case reported off-label use in a pediatric patient <1 year.

Our review of the DECs reported in the 16 U.S. FAERS cases with rufinamide did not identify any new safety concerns. The majority of reported DECs were consistent with the known risks described in the labeling, and no apparent increased severity was observed in these cases. Some labeled DECs were related to skin events, gastrointestinal disorders, specific seizure types, and central nervous system effects. These adverse events are adequately described in the labeling.

We identified three foreign pediatric FAERS cases reporting three unlabeled adverse events, i.e., hyperammonemia, rhabdomyolysis and agranulocytosis. These three cases suggested a possible causal association because of the temporal association; however, two of the three cases reported alternative causes for the adverse events, i.e., overdose and underlying disease. The third case reported agranulocytosis occurring 17 days after adding rufinamide to existing valproate and lamotrigine therapy; agranulocytosis resolved after discontinuing rufinamide. We did not identify any additional FAERS cases of agranulocytosis in all ages since its initial approval in 2008.

4 CONCLUSION

Our data does not suggest a new pediatric safety concern with rufinamide at this time.

5 RECOMMENDATION

We will continue postmarketing surveillance of all adverse events associated with the use of rufinamide including agranulocytosis in all patient populations.

6 REFERENCES

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4. Ide M, Kato T, Nakata M, et al. Agranulocytosis associated with rufinamide: A case report. Brain and Development. 2015;37(8):825-828.

7 APPENDICES

7.1 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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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 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.

Data Mining Of FAERS Using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

7.2 APPENDIX B. LIST OF OSE DESIGNATED MEDICAL EVENTS AND ASSOCIATED MEDDRA PTS

Designated Medical Event	MedDRA Preferred Terms (Version 19.1)
Acute pancreatitis	Pancreatic necrosis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis, Haemorrhagic necrotic pancreatitis
Acute respiratory failure	Acute respiratory distress syndrome, Acute respiratory failure, Respiratory failure
Agranulocytosis	Agranulocytosis, Febrile neutropenia, Neutropenia
Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Anaphylaxis and anaphylactoid reactions	Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Anaphylactic transfusion reaction
Aplastic anemia	Aplasia pure red cell, Aplastic anemia, Bone marrow failure
Blind	Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Sudden visual loss
Colitis ischaemic	Colitis ischaemic, Intestinal infarction
Congenital anomalies	Congenital anomaly
Deaf	Deafness bilateral, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness unilateral, Deafness, Sudden hearing loss
Disseminated intravascular coagulation	Disseminated intravascular coagulation
Endotoxic shock, confirmed or suspected	Endotoxic shock, Septic shock
Haemolysis	Haemoglobinaemia, Haemoglobinuria, Haemolysis, Haptoglobin decreased, Intravascular haemolysis
Hemolytic anemia	Coombs negative haemolytic anaemia, Coombs positive haemolytic anaemia, Haemolytic anaemia
Liver failure	Acute hepatic failure, Hepatic encephalopathy, Hepatic failure, Subacute hepatic failure
Liver necrosis	Hepatitis acute, Hepatitis fulminant, Hepatic necrosis
Liver transplant	Liver transplant
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome

Designated Medical Event	MedDRA Preferred Terms (Version 19.1)
Pancytopenia	Pancytopenia
Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Product infectious disease transmission	Suspected transmission of an infectious agent via product, Transmission of an infectious agent via product, Product contamination microbial
Pulmonary fibrosis	Pulmonary fibrosis
Pulmonary hypertension	Cor pulmonale, Pulmonary hypertension
Renal failure	Renal failure, Acute kidney injury, Renal impairment
Rhabdomyolysis	Rhabdomyolysis
Seizure	Seizure, Epilepsy, Generalized tonic-clonic seizure
Serotonin syndrome	Serotonin syndrome
Stevens-Johnson syndrome	Erythema multiforme, Stevens-Johnson syndrome
Sudden death	Sudden cardiac death, Sudden death
Suicide	Completed suicide
Torsade de Pointes	Torsade de pointes
Toxic epidermal necrolysis	Dermatitis exfoliative, Toxic epidermal necrolysis
TTP	Thrombotic thrombocytopenic purpura
Ventricular fibrillation	Ventricular fibrillation

7.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH RUFINAMIDE (N=16)

FAERS#	Version#	MFR Ctrl #
10062259	1	E2080-00620-SPO-US
10062271	1	E2080-00611-SPO-US
10688794	1	US-AUROBINDO-AUR-APL-2014-13746
10938909	2	US-JNJFOC-20140401813
11138725	1	PHHY2015US062564
11217538	1	PHHY2015US056358
11413713	1	US-PFIZER INC-2015277340
11538718	1	Direct Report
11650531	1	US-LUNDBECK-DKLU2005392
11754312	1	US-EISAI MEDICAL RESEARCH-EC-2015-012144
11798437	2	US-LUNDBECK-DKLU2006277
11922258	3	US-LUNDBECK-DKLU2008744
11971724	1	US-EISAI MEDICAL RESEARCH-EC-2016-013909
12548633	1	US-TEVA-580907USA
13232365	1	US-EISAI MEDICAL RESEARCH-EC-2017-024873
9882712	3	US-LUNDBECK-DKLU1097213

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