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Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for vigabatrin in pediatric patients.

On October 26, 2013, FDA approved Sabril® (vigabatrin) as adjunctive therapy for refractory complex partial seizures (CPS) in pediatric patients 10 years and older who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of vision loss. Vigabatrin was previously approved as monotherapy for the treatment of infantile spasms in children 1 month to 2 years of age.

With respect to drug utilization data, we found majority of total sales of vigabatrin was distributed through the mail order pharmacy setting. During the 12-month period ending in July 2015, pediatric patients (0-16 years) accounted for majority (approximately 3,500 pediatric patients/4,300 total patients) of the patients receiving a prescription for vigabatrin from outpatient mail-order pharmacies. The majority of pediatric use was in children less than 6 years of age accounting for over two-thirds (approximately 2,500 pediatric patients) of total pediatric patients. This pediatric use distribution is consistent with U.S. serious FAERS reports included in this review, where the majority of these reports also involved children less than 6 years of age. Vigabatrin use has roughly doubled for all pediatric age groups across the years from 1,900 pediatric patients to 3,500 pediatric patients by 12-month period ending in July 2015. Neurologists were the top prescribing group, followed by pediatricians. U.S. office-based physician surveys data did not report any diagnoses associated with vigabatrin use in pediatric patients.

We identified 1,001 serious U.S. FAERS pediatric reports with vigabatrin that were received from August 1, 2013 to July 31, 2015, including 154 cases reporting an outcome of death. The 154 cases reporting an outcome of death described 87 drug-event combinations (DECs). The majority of the serious reports other than death described labeled adverse events. We identified four events of special interest for further review (received from August 21, 2009 to July 31, 2015). The events of special interest included blindness (unlabeled), renal events (unlabeled), pancreatitis (unlabeled), and abnormal MRI (labeled).

The 154 cases reporting an outcome of death described disease progression, infection, respiratory insufficiency, or underlying congenital disorders. Clinical details surrounding death were not well-described or the cases contained insufficient information to assess causality. The 68 cases reporting the events of special interest (blindness and abnormal MRI) were consistent with the known risk in the labeling. Although medical history, concomitant medication, or diet may have contributed to renal events and pancreatitis, we could not rule out the role of vigabatrin.

Our evaluation of the 154 U.S. FAERS cases reporting an outcome of death and 68 cases reporting the events of special interest does not suggest any new or unexpected pediatric safety concerns with vigabatrin at this time. DPV will continue postmarketing surveillance of all adverse events with the use of vigabatrin in pediatric patients.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Sabril® (vigabatrin), an irreversible inhibitor of gamma-aminobutyric acid (GABA) transaminase, is approved in the U.S. for the treatment of:

- Refractory Complex Partial Seizures (CPS) in patients ≥10 years of age; Sabril should be used as adjunctive therapy in patients who have responded inadequately to several alternative treatments
- Infantile Spasms - monotherapy in infants 1 month to 2 years of age

Vigabatrin is available as a tablet and a powder for oral solution:

- NDA 20-427: tablets, for oral use (500 mg)
- NDA 22-006: powder for oral solution (500 mg)

Vigabatrin was first approved in the United Kingdom in 1989, and has been marketed in other countries since then. On August 21, 2009, FDA granted vigabatrin an orphan status designation as monotherapy for the treatment of infantile spasms in infants (1 month to 2 years of age). On October 26, 2013, FDA approved vigabatrin for CPS in pediatric patient population (≥10 years of age). Vigabatrin was approved for patients in whom the potential benefits outweigh the potential risk of vision loss.

1.2 THE SUPPORT, HELP AND RESOURCES FOR EPILEPSY (SHARE) REGISTRY

At the time of original approval, August 21, 2009, FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary for vigabatrin to ensure the benefits of the drug outweigh the risks of vision loss and of suicidal thoughts and behaviors. The REMS includes a Medication Guide, Communication Plan, Elements to Assure Safe Use, and Implementation System.[1] The REMS seeks to mitigate the risk of permanent vision loss in part through required periodic visual monitoring (documented by ophthalmologic assessment forms) and early benefit-risk assessment (documented by treatment maintenance forms). In September 2009, a prospective registry was developed as part of the overall REMS postmarketing requirement for vigabatrin. The Support, Help and Resources for Epilepsy (SHARE) registry includes all patients in the U.S. who may be prescribed vigabatrin.

As of August 25, 2015, (b) (4) patients of all ages were enrolled in the SHARE Registry Program, including (b) (4) males and (b) (4) females. Reported reasons for vigabatrin use (provided by prescribers) were (b) (4) . **Note:** Lundbeck LLC provided to FDA this proprietary information, which cannot be released to the public/non-FDA personnel without approval obtained through the FDA.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current approved labeling for vigabatrin (November 4, 2015) provides the following information excerpted from pertinent sections:[2]

BOXED WARNING: VISION LOSS

- SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity (5.1).
- Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss (5.1).
- Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL (5.1).
- Unless a patient is formally exempted, periodic vision assessment is required for patients on SABRIL.
- However, this assessment cannot always prevent vision damage (5.1).
- SABRIL can cause permanent vision loss. SABRIL is available only through a restricted program called the SHARE Program (5.2).

WARNINGS AND PRECAUTIONS

- Abnormal MRI signal changes have been reported in some infants with Infantile Spasms receiving SABRIL (5.3)
- Suicidal behavior and ideation: Antiepileptic drugs, including SABRIL, increase the risk of suicidal thoughts and behavior (5.5)
- Withdrawal of AEDs: Dose should be tapered gradually to avoid withdrawal seizures (5.6)
- Anemia: Monitor for symptoms of anemia (5.7)

ADVERSE REACTIONS

Refractory Complex Partial Seizures

Most common adverse reactions in controlled studies include (incidence ≥5% over placebo):

- Adults: in addition to permanent vision loss, fatigue, somnolence, nystagmus, tremor, blurred vision, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state (6.1)
- Pediatric patients (10 to 16 years of age): weight gain, upper respiratory tract infection, tremor, fatigue, aggression, and diplopia (6.1)

Infantile Spasms (incidence >5% and greater than on placebo)

Somnolence, bronchitis, ear infection, and acute otitis media (6.1)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the Agency to conduct this analysis. **Appendix A** includes detailed descriptions of the databases.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the setting by which vigabatrin is distributed from August 1, 2012 through July 31, 2015. Sales distribution data for vigabatrin in bottles or packets[a] sold from the manufacturer to all U.S. retail and non-retail channels of distribution showed that approximately 95% of vigabatrin products were sold to mail order pharmacies; 5% was sold to non-retail settings, mainly to home health care. No sales were captured as distributed to retail pharmacies.[b] Pharmacies that dispense vigabatrin are specially certified by the Sponsor under the approved REMS program.[1] Based on these results, we examined the drug utilization patterns for vigabatrin in mail order pharmacies. Drug use data for non-retail (e.g. home healthcare, clinics) or retail settings are not included in this review.

2.1.2 Data Sources Used

The Symphony Health Solutions' PHAST Patient Monthly database was used to obtain the nationally estimated number of patients with a prescription claim for vigabatrin from mail order pharmacies, stratified by patient age (0-1, 2-5, 6-11, 12-16, 17-64, and 65 years and older) from August 2012 through July 2015, annually.

The IMS, National Prescription Audit (NPA) database was used to obtain the nationally estimated number of prescriptions dispensed for vigabatrin from mail order pharmacies, stratified by prescriber specialty, from August 2012 through July 2015, aggregated.

The Encuity Research, LLC, Treatment Answers™, a U.S. office-based physician survey database was used to obtain the top diagnoses associated with the use of vigabatrin, stratified by patient age (0-1, 2-5, 6-11, 12-16, 17-64, and 65 years and older), from August 2012 through July 2015, aggregated. Diagnoses data by number of drug use mentions[c] were captured based on International Classification of Diseases (ICD-9-CM) codes.

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[a] Sabril (vigabatrin) is supplied as 500 mg tablets in bottles of 100 (NDC 67386-111-01) or as 500 mg packets (granular powder) in packages of 50 (NDC 67386-211-65).

[b] IMS Health, IMS National Sales Perspectives™ Database. August 2012 – July 2015. Extracted September-2015. File: NSP 2015-1947 Channels Vigabatrin BPCA Sept-2015.

[c] The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is

2.2 RESULTS

2.2.1 Patient Demographics

Table 1 and Figure 1 provide the nationally estimated number of unique patients receiving a prescription for vigabatrin from mail-order pharmacies, stratified by patient age from August 2012 through July 2015, annually. During the 12-month period ending in July 2015, a total of approximately 4,300 patients received a prescription for vigabatrin from mail-order pharmacies. Of the total patients, pediatric patients aged 0-16 years accounted for majority (81%, 3,500 patients) of the patients receiving a prescription for vigabatrin during the examined time.

Pediatric patients aged 0-1 year accounted for 36% (1,200 patients) of the total pediatric patients receiving a prescription for vigabatrin during the examined time and 2-5 year age group accounted for 37% (1,300 patients) of pediatric patients. This was followed by patients aged 6-11 years at 18% (600 patients) and patients aged 12-16 years at 9% (300 patients) of the total pediatric patients.

Table 1. Nationally Estimated Number of Patients Dispensed Prescription for Sabril (vigabatrin), Stratified by Patient age, from U.S. Mail Order Pharmacies, August 1, 2012 - July 31, 2015

	Aug 2012 - July2013		Aug 2013 - July 2014		Aug 2014 - July 2015	
	Patients N	Share %	Patients N	Share %	Patients N	Share %
SABRIL TOTAL PATIENTS	**2,342**	**100.0%**	**3,497**	**100.0%**	**4,279**	**100.0%**
0 - 16 years	**1,872**	**79.9%**	**2,801**	**80.1%**	**3,463**	**80.9%**
0 - 1 years	541	28.9%	995	35.5%	1,242	35.9%
2 - 5 years	784	41.9%	1,040	37.1%	1,266	36.6%
6 - 11 years	363	19.4%	510	18.2%	636	18.4%
12 - 16 years	184	9.8%	257	9.2%	318	9.2%
17 -64 years	**461**	**19.7%**	**676**	**19.3%**	**787**	**18.4%**
65+ years	**8**	**0.3%**	**20**	**0.6%**	**29**	**0.7%**

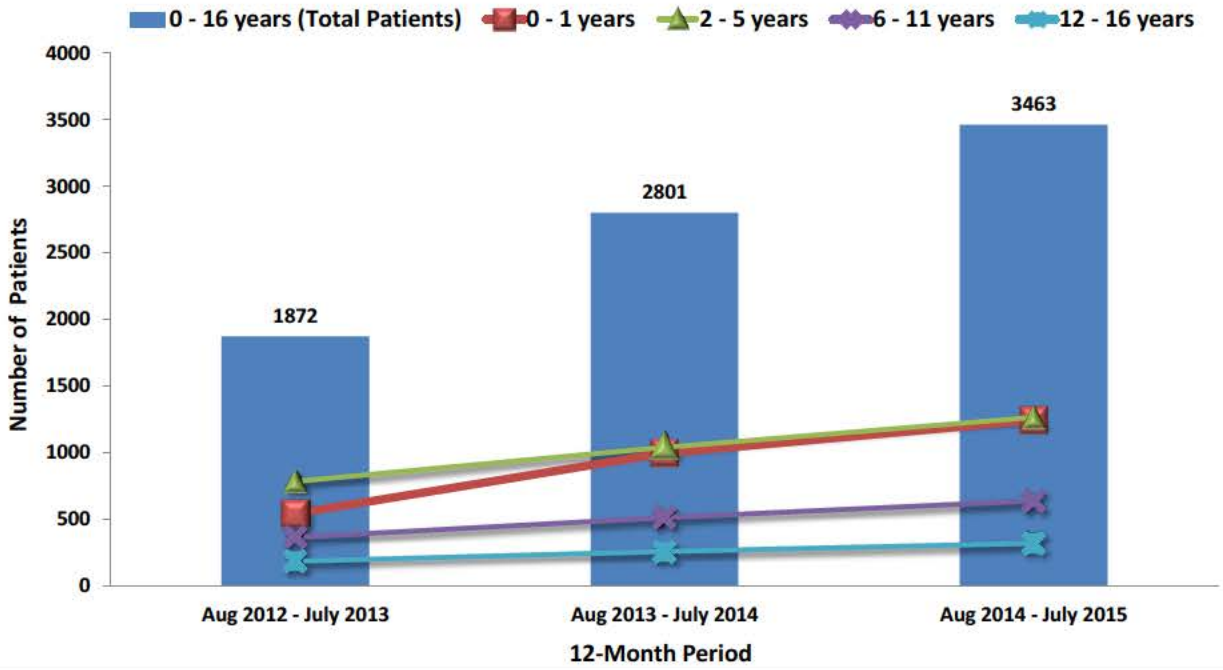
Source Symphony Health Solutions' PHAST Patient Monthly. Years 2012 - 2015. Extracted Sept-2015.
File SHSPAT 2015-1947 Vigabatrin BPCA Sept-2015.xlsx

Note: Subtotals may not sum exactly because of patients aging during the study period, and may be counted more than once in the individual age categories. Therefore, summing across patient age bands is not advisable and will result in overestimates of patient counts.

The total number of patients receiving vigabatrin almost doubled from 2,300 patients during the 12-month period ending in July 2013 to 4,300 patients during the 12-month period ending in July 2015. A similar drug use pattern was observed across all pediatric age groups (0-16 years), from 1,900 patients to 3,500 patients during the same examined time period ending in July 2015.

important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Figure 1. Nationally Estimated Number of Pediatric Patients (0-16) With a Dispensed Prescription for Sabril (vigabatrin) From U.S. Mail Order Pharmacies From August 1, 2012 to July 31, 2015



Source: Symphony Health Solutions' PHAST Patient Monthly. Years 2012 - 2015. Extracted Sept-2015.
File: SHSPAT 2015-1947 Vigabatrin BPCA Sept-2015.xlsx

2.2.2 Prescriber Specialty

Table 2 provides the nationally estimated number of prescriptions dispensed for vigabatrin from U.S. mail order pharmacies, stratified by prescriber specialty, from August 2012 through July 2015, aggregated. During the examined time period, approximately 71,400 prescriptions were dispensed for vigabatrin. Neurology was the top prescribing specialty accounting for approximately 77% (55,000 prescriptions) of total vigabatrin prescriptions dispensed followed by pediatric specialties, accounting for 9% (6,400 prescriptions) of total prescriptions dispensed for vigabatrin.

Table 2. Total Number of Prescriptions for Sabril (vigabatrin) Dispensed through U.S Mail Order Pharmacies, by Top Prescribing Specialties, August 1, 2012 - July 31, 2015

PRESCRIBER SPECIALTY	PRESCRIPTIONS (N)	SHARE (%)
VIGABATRIN TOTAL PRESCRIPTIONS	71,411	100.0%
NEUROLOGY	55,055	77.1%
PEDIATRICS	**6,436**	**9.0%**
NURSE PRACTITIONER	3,786	5.3%
CLINICAL NEUROPHYSIOL	2,048	2.9%
OSTEOPATHIC MEDICINE	1,987	2.8%
ALL OTHERS	2,099	2.9%

Source IMS, National Prescription Audit (NPA). Aug 2012 - July 2017 Extracted October 2015.
File: NPA 2015-1947 Specialty Vigabatrin BPCA Oct-2015.xlsx

2.2.3 Diagnoses Associated with Use

No diagnosis data associated with the use of vigabatrin in pediatric patients aged 0-16 years were captured in the U.S. office-based physician survey database during the examined study period.[d]

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

We identified all U.S. pediatric cases reporting a serious outcome (received from August 1, 2013 to July 31, 2015). Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. We reviewed all U.S. pediatric cases reporting the outcome of death (received from August 1, 2013 to July 31, 2015) (**Section 3.3**). Additionally, we screened all reported DECs and identified four events of special interest for further review (received from August 21, 2009 to July 31, 2015). The events of special interest included blindness, abnormal MRI, renal events, and pancreatitis (**Section 3.4.1**).

Appendix B describes the characteristics of U.S. serious pediatric reports other than death for vigabatrin (received from August 1, 2013 to July 31, 2015).

[d] *Source: Encuity Research , LLC Treatment Answers™. August 2012- July 2015. Extracted 2015. File: Encuity 2015-1947 Vigabatrin BPCA Oct-2015.xlsx*

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

We searched the FAERS database with the strategy described in **Table 3.**

Appendix C describes the FAERS database.

Table 3. FAERS Search Strategy	
Date of Search	August 27, 2015
Time Period of Search	August 1, 2013* - July 31, 2015
Product Name(s)	Product Name: Sabril Active Ingredient: Vigabatrin
Search Parameters	All ages, all outcomes, worldwide

* Time period corresponds to two years of US drug utilization data

3.2 RESULTS

3.2.1 Total number of FAERS Reports by Age

Table 4 summarizes total number of reports.

Table 4. U.S. FAERS Reports Indicating Serious Outcomes for Vigabatrin (Received by FDA From August 1, 2013 to July 31, 2015) *

	All reports (US)	**Serious† (US)**	**Death (US)**
Adults (≥ 17 years)	429 (409)	283 (263)	35 (35)
Pediatrics (0 - <17 years)	1305 (1243)	903 **(847)**	165 **(158)** ‡

* May include duplicates and transplacental exposures, and have not been assessed for causality

† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

‡ 50 additional cases of pediatric deaths were identified among cases not reporting an age.

3.3 SUMMARY OF U.S. PEDIATRIC CASES REPORTING AN OUTCOME OF DEATH (N=154)

We identified 158 U.S. FAERS pediatric cases (received from August 1, 2013 to July 31, 2015) reporting an outcome of death with vigabatrin. We excluded 4 duplicate cases. The remaining 154 unique cases reported 87 DECs. 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.

Appendix D lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the U.S. fatal pediatric cases.

Table 5 summarizes the 154 U.S. pediatric cases reporting an outcome of death with vigabatrin.

Table 5. Characteristics of U.S. FAERS Pediatric Cases Reporting an Outcome of Death for Vigabatrin (Received by FDA From August 1, 2013 to July 31, 2015), (N=154) [*]		
Age n=154	0 - < 1 month 1 month - <2 years 2- < 6 years 6- <12 years 12- < 17 years	1 69 61 17 6
Sex n=150	Male Female	79 71
Total Daily Dose (mg) n=146	Range Median Mean	150-6000 1200 1438
Reason for Use n=147	Infantile spasms Partial seizures Generalized seizures Seizures/epilepsy NOS Tuberous Sclerosis	121 11 4 9 2
Time-to-Death [†] n=100	Range Median Mean	1 day-7.9 years 1.1 years 1.7 years
Cause of Death (System Organ Class)	Unknown Respiratory, Thoracic and Mediastinal Disorders [‡] Cardiac Disorders [§] Nervous System Disorders[‖] General Disorders and Administration Site Conditions [¶] Infections and Infestations [**] Surgical and Medical Procedures[††] Vascular Disorders [‡‡]	106 24 10 10 1 1 1 1

[*] Reported information extracted from the narrative field
[†] Time from the initial drug exposure to death (approximates duration of therapy)
[‡] Respiratory failure, respiratory distress, respiratory issues, aspiration pneumonia
[§] Cardiac arrest, cardio-respiratory arrest, heart failure
[‖] Encephalopathy, seizures/epilepsy, neurological disease, underlying brain malformation
[¶] Natural causes
[**] Sepsis
[††] Withdrawal of life support
[‡‡] Circulatory collapse

Table 6 summarizes the 154 U.S. pediatric cases reporting an outcome of death with vigabatrin, categorized by reported reason for use.

Table 6. Characteristics of U.S. FAERS Pediatric Cases Reporting an Outcome of Death for Vigabatrin by Reported Reason for use (Received by FDA From August 1, 2013 to July 31, 2015), (N=145) [*]

Reason for Use		Infantile spasms (n=121)	Seizures/ Epilepsy (n=24)
Age	≤ 2 years	66	7
n=145	3-10 years	51	12
	>10 years	4	5
Sex	Male	62	11
n=141	Female	55	13
Total Daily Dose (mg) [†]	Range	300-6000	450-4500
n=141	Median	1000	2000
	Mean	1264	2002
Dosing Frequency	Once	11	6
(per day)	Twice	101	14
n=141	Three times	6	2
	Four times	0	1
Time-to-Death [‡]	Range	2 days-5.9 years	1 day-7.9 years
n=99	Median	1 year	2.1 years
	Mean	1.5 years	2.4 years

[*] Reported information extracted from the narrative field; 2 patients with tuberous sclerosis not included

[†] Recommended dose in infantile spasms patients (1 month-2 years of age): 25mg/kg twice daily (maximum 75mg/kg twice daily); in CPS patients (10-16 years of age): (25-60kg): 250mg twice daily (maximum 1000mg twice daily) and (> 60kg): 1500mg twice daily

[‡] Should be withdrawn if it fails to show substantial clinical benefit within 2-4 weeks in infantile spasms patients and within 3 months in CPS patients

We grouped the 154 cases reporting an outcome of death by system organ class (SOC): general disorders and administration site conditions (n=111), respiratory, thoracic and mediastinal disorders (n=30), nervous system disorders (n=25), infections and infestations (n=20), cardiac disorders (n=10), metabolism and nutrition disorders (n=6), congenital, familial and genetic disorders (n=4), gastrointestinal disorders (n=4), injury, poisoning and procedural complications (n=3), vascular disorders (n=3), investigations (n=2), and renal and urinary disorders (n=1). *Each case can appear in more than one SOC.*

The 154 cases reporting an outcome of death described disease progression, infection, respiratory insufficiency, and underlying congenital disorders, such as Aicardi's, Cockayne, Dandy-Walker, Miller-Diecker, Ohtahara, and Leigh syndrome, as possible contributory factors. Clinical details surrounding death were not well-described or the cases contained insufficient information to assess causality.

3.3.1 General Disorders and Administration Site Conditions (n=111)

[Patient age: range 3 months-16 years (mean 3.4 years; median 2 years)]

One hundred and eleven cases reported the events of death (n=107), disease complication (n=2), pyrexia (n=1), or asthenia (n=1). Reported age ranged from 3 months to 16 years (mean 3.4 years; median 2 years). Vigabatrin total daily dose ranged from 300 mg to 6000 mg (mean 1500 mg ; median 1250 mg) and was used for the treatment of infantile spasms (n=87), seizures/epilepsy NOS (n=7), partial seizures (n=6), generalized seizures (n=4), and tuberous sclerosis (n=1). Time-to-death reported in 65 cases ranged from 2 days to 2880 days (mean 651 days; median 472 days). Of the 107 cases reporting death, 89 contained insufficient clinical information surrounding death; these cases reported the DEC of death only. The cause of death was reported as "unknown." Thirty-four cases reported a medical history of developmental delay and neurological impairment (n=30) and neuro-metabolic disorders (n=6). Fifty-six cases reported the concomitant use of at least one of the following: levetiracetam (n=32), topiramate (n=25), phenobarbital (n=15), clobazam (n=11), zonisamide (n=8), ACTH (n=8), divalproex (n=6), phenytoin (n=4), rufinamide (n=3), valproic acid (n=2), oxcarbazepine (n=2), lacosamide (n=2), felbamate (n=2), and lamotrigine (n=2).

3.3.2 Respiratory, Thoracic and Mediastinal Disorders (n=30)

[Patient age: range 6 days-12 years (mean 2.9 years; median 2.1 years)]

Thirty cases reported the events of respiratory failure (n=12), pneumonia/pneumothorax (n=8), respiratory distress and hypoxia (n=5), respiratory arrest (n=4), or pulmonary hypertension (n=1). Reported age ranged from 6 days to 12 years (mean 2.9 years; median 2.1 years). Vigabatrin total daily dose ranged from 300 mg to 3400 mg (mean 1250 mg; median 1000 mg) and was used for the treatment of infantile spasms (n=25), partial seizures (n=3) and seizures/epilepsy NOS (n=1). Time-to-death reported in 18 cases ranged from 47 days to 1440 days (mean 418 days; median 330 days). Twenty-eight cases reported a medical history of severe developmental delay and neurological impairment (n=25), respiratory insufficiency/failure (n=7), cerebral palsy (n=3), and obstructive sleep apnea (n=3). Twenty-two cases reported the concomitant use of at least one of the following: levetiracetam (n=11), phenobarbital (n=5), topiramate (n=9), clobazam (n=7), divalproex (n=4) zonisamide (n=3), ACTH (n=3), valproic acid (n=3), rufinamide (n=2), phenytoin (n=2), oxcarbazepine (n=2), lacosamide (n=2), felbamate (n=1), and lamotrigine (n=1).

3.3.3 Nervous System Disorders (n=25)

[Patient age: range 6 days-12 years (mean 2.5 years; median 1.4 years)]

Twenty-five cases reported the events of seizures (n=23), neuromuscular disorders (n=1), or disturbances in consciousness (n=1). Reported age ranged from 6 days to 12 years (mean 2.5 years; median 1.4 years). Vigabatrin total daily dose ranged from 150 mg to 3000 mg (mean 1150 mg; median 1000 mg). The reported reason for use was infantile spasms (n=20), and partial seizures (n=4). Time-to-death reported in 16 cases ranged from 1 day to 1350 days (mean 415 days; median 180 days). Twenty-one cases reported a medical history of severe

developmental delay and neurological impairment. Eighteen cases reported the concomitant use of at least one of the following: levetiracetam (n=10), clobazam (n=7), topiramate (n=5), phenobarbital (n=4), divalproex (n=2), rufinamide (n=2), valproic acid (n=2), lacosamide (n=2), ACTH (n=2), zonisamide (n=1), felbamate (1), lamotrigine (n=1), and oxcarbazepine (n=1).

3.3.4 Infections and Infestations (n=20)

[Patient age: range 7 months-7 years (mean 3.1 years; median 3 years)]

Twenty cases reported the events of pneumonia (n=13), viral infections (n=3), bacterial infections (n=2), or pathogen unspecified infections (n=2). Reported age ranged from 7 months to 7 years (mean 3.1 years; median 3 years). Vigabatrin total daily dose ranged from 400 mg to 3400 mg (mean 1470 mg ; median 1500 mg) and was used for the treatment of infantile spasms (n=18), partial seizures (n=1), and seizures/epilepsy NOS (n=1). Time-to-death reported in 16 cases ranged from 85 days to 1500 days (mean 601 days; median 405 days). Sixteen cases reported a medical history of severe developmental delay and neurological impairment (n=12), congenital anomaly (n=6), respiratory insufficiency (n=5), and blindness (n=4). Twelve cases reported the concomitant use of at least one of the following: levetiracetam (n=6), topiramate (n=5), divalproex (n=4), valproic acid (n=3), ACTH (n=3), zonisamide (n=2), clobazam (n=1), and carbamazepine (n=1).

3.3.5 Cardiac Disorders (n=10)

[Patient age: range 6 months-11.5 years (mean 3.1 years; median 2.3 years)]

Ten cases reported the events of cardiac arrest (n=8), cardiac failure (n=1), or tachycardia (n=1). Reported age ranged from 6 months to 12 years (mean 3.1 years; median 2.3 years). Vigabatrin total daily dose ranged from 300 mg to 3400 mg (mean 1270 mg ; median 1000 mg) and was used for the treatment of infantile spasms (n=8), partial seizures (n=1), and tuberous sclerosis (n=1). Time-to-death reported in 6 cases ranged from 78 days to 1800 days (mean 540 days; median 358 days). Nine cases reported a medical history of severe developmental delay and neurological impairment (n=8) and respiratory insufficiency (n=1). Six cases reported the concomitant use of at least one of the following: levetiracetam (n=3), phenobarbital (n=3), clobazam (n=2), and felbamate (n=1).

3.3.6 Metabolism and Nutrition Disorders (n=6)

[Patient age: range 10 months-3.9 years (mean 2.2 years; median 2.2 years)]

Six cases reported the events of feeding/metabolic disorder (n=4) or dehydration (n=2). Reported age ranged from 10 months to 3.9 years (mean 2.2 years; median 2.2 years). Vigabatrin total daily dose ranged from 1000 mg to 3400 mg (mean 1780 mg ; median 1500 mg) and was used for the treatment of infantile spasms (n=5). Time-to-death reported in 1 case was 85 days. Six cases reported a medical history of neurological impairment (n=5) and respiratory insufficiency (n=1). Two cases reported the concomitant use of the following: levetiracetam (n=1) and ACTH (n=1).

3.3.7 Congenital, Familial and Genetic Disorders (n=4)

[Patient age: range 1.8-5.1 years (mean 3.0 years; median 2.6 years)]

Four cases reported the events of neurological disorders (n=3) or congenital disorders (n=1). Reported age ranged from 1.8 years to 5.1 years (mean 3.0 years; median 2.6 years). Vigabatrin total daily dose ranged from 750 mg to 2000 mg (mean 1190 mg ; median 1000 mg) and was used for the treatment of infantile spasms (n=4). Time-to-death reported in 4 cases ranged from 150 days to 1350 days (mean 668 days; median 585 days). Three cases reported a medical history of Down syndrome (n=1), West syndrome (n=1) and Dravet syndrome (n=1). Four cases reported the concomitant use of at least one of the following: levetiracetam (n=3), zonisamide (n=2), phenobarbital (n=1), clobazam (n=1), topiramate (n=1), and lacosamide (n=1).

3.3.8 Gastrointestinal Disorders (n=4)

[Patient age: range 1.4-4.1 years (mean 2.4 years; median 2.2 years)]

Four cases reported the events of mouth ulceration (n=1), vomiting (n=1), ileus (n=1), or acute abdomen (n=1). Reported age ranged from 1.4 years to 4.1 years (mean 2.4 years; median 2.2 years). Vigabatrin total daily dose ranged from 400 mg to 1000 mg (mean 800 mg ; median 900 mg) and was used for the treatment of infantile spasms (n=4). Time-to-death ranged from 85 days to 730 days (mean 486 days; median 570 days). Three cases reported a medical history of developmental delay. Two cases reported the concomitant use of at least one of the following: levetiracetam (n=2), phenobarbital (n=1), topiramate (n=1), lacosamide (n=1), and clobazam (n=1).

3.3.9 Injury, Poisoning and Procedural Complications (n=3)

[Patient age: range 11 months-2.7 years (mean 1.7 years; median 1.4 years)]

Three cases reported the events of drug dose omission (n=2) or stoma site reaction (n=1). Reported age ranged from 11 months to 2.7 years (mean 1.7 year; median 1.4 years). Vigabatrin total daily dose ranged from 600 mg to 1400 mg (mean and median 1000 mg) and was used for the treatment of infantile spasms (n=3). Time-to-death reported in 2 cases was 180 days and 720 days (mean and median 900 days). Three cases reported a medical history of developmental delay (n=3), multiple congenital anomalies (n=1), and failure to thrive (n=1) and the concomitant use of at least one of the following: levetiracetam (n=2), topiramate (n=2), phenobarbital (n=1), clobazam (n=1), divalproex (n=1), rufinamide (n=1), ACTH (n=1), and valproic acid (n=1).

3.3.10 Vascular Disorders (n=3)

[Patient age: range 1.7 years-4.5 years (mean 3.1 years; median 3 years)]

Three cases reported the events of shock (n=1), hypotension (n=1), or pulmonary hypertension (n=1). Reported age ranged from 1.7 years to 4.5 years (mean 3.1 years; median 3 years).

Vigabatrin total daily dose ranged from 800 mg to 3400 mg (mean 1980; median 1750 mg) and was used for the treatment of infantile spasms (n=3). Time-to-death reported in 2 cases was 330 days and 420 days (mean and median 375 days). All cases reported a medical history of developmental delay (n=2), visual impairment/blindness (n=2), and respiratory issues (n=1). One case reported the concomitant use of levetiracetam.

3.3.11 Investigations (n=2)

[Patient age: range 8 months-10 months (mean and median 9 months)]

Two cases reported the events of increased oxygen consumption (n=1) or an abnormal brain MRI (n=1). Reported age ranged from 8 months to 10 months (mean and median 9 months). Vigabatrin total daily dose ranged from 650 mg to 1750 mg (mean and median 1200 mg) and was used for the treatment of infantile spasms (n=2). Time-to-death reported in 1 case was 150 days. Both cases reported a medical history of Leigh syndrome. Two cases reported the concomitant use of at least one of the following: clobazam (n=1), topiramate (n=1), and ACTH (n=1).

3.3.12 Renal and Urinary Disorders (n=1)

[Patient age: 8.7 years]

One case reported an event of renal impairment. Reported age was 8.7 years. Vigabatrin total daily dose was 1000 mg and was used for the treatment of infantile spasms. Time-to-death was 1260 days. The case reported a medical history of chronic kidney disease stage 4, hypertension, urinary sediment, anemia, bone marrow failure, Leigh syndrome and developmental delay and the concomitant use of levetiracetam, felbamate, and lamotrigine.

3.4 SUMMARY OF SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST (N=68)

We identified blindness, abnormal MRI, renal events, and pancreatitis as events of special interest for further review. For these events, we reviewed reports submitted to the FAERS database from August 21, 2009 to July 31, 2015.

Appendix E lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the U.S. serious events of special interest.

3.4.1 Unlabeled Event: Blindness (n=28)

[Patient age: range 4 months-14 years (mean 3.7 years; median 2)]

Vigabatrin is not labeled for blindness. However, it is labeled for “Vision Loss” in the Boxed Warning and Warnings and Precautions Sections. We reviewed the event of blindness as a possible event of higher severity. The events reported in this pediatric case series were consistent with the known risk in the labeling.

Twenty-eight cases reported the event of blindness. Two cases reported disability. Reported age ranged from 4 months to 14 years (mean 3.7 years; median 2 years). Vigabatrin total daily dose reported in 19 cases ranged from 150 mg to 3000 mg (mean 1400 mg; median 1500 mg) and was used for the treatment of infantile spasms (n=14), seizures/epilepsy NOS (n=3), partial seizures (n=1), and encephalopathy (n=1). Time-to-event reported in 10 cases ranged from 63 days to 1460 days (mean 677 days; median 600 days). Twenty-two cases reported ophthalmologic assessment (OA) as either being conducted (n=18) or exempted (n=4). The reported reasons for the OA exemption were cortical blindness (n=3) and an unspecified neurologic disorder (n=1). Action taken with vigabatrin was reported as ongoing (n=13), discontinued (n=9), or unknown (n=6).

Of the 28 cases reporting the event of blindness, 2 cases experienced the event prior to vigabatrin treatment. Eighteen cases had insufficient information on medical history, concomitant medications, and provided minimal information of the event (e.g., "patient appears blind" or "patient's condition precluded the need for visual assessment"). Although the remaining eight cases may have insufficient information on medical history and concomitant medications, these eight cases provide evidence of visual loss progression (baseline and follow-up exams) or describe visual loss progression; therefore, we cannot rule out the role of vigabatrin. The eight cases are described below.

FAERS #9253147v3
A 15-month-old male was reported to have unilateral blindness (right eye optic atrophy) during an OA. Vigabatrin (dose unknown) was administered for the treatment of epilepsy NOS. Time-to-event was approximately nine months. Two follow-up OAs conducted at one-year intervals described the same visual field test results. Vigabatrin treatment was continued. Medical history included tuberous sclerosis, infantile spasms, and nonverbal. Concomitant medications included phenobarbital and topiramate.

FAERS #10063570v3
A 20-month-old female experienced new optic atrophy during an OA. Fundoscopic examination revealed pale optic discs, peripheral pigmentary mottling in each eye, cortical visual impairment, and retinal toxicity. Vigabatrin (dose unknown) was administered for an unknown indication. Time-to-event was unknown. The follow-up OA described the patient as legally blind and further exempt from OAs. Vigabatrin treatment was continued. Medical history included hydrocephalus, ventriculo-peritoneal shunt, lissencephaly, and developmental psychomotor impairment. Concomitant medications included zonisamide and phenobarbital.

FAERS #10656480v2
A 22-month-old male experienced visual changes during an OA. Vigabatrin total daily dose was 1500 mg and was used for the treatment of infantile spasms. Time-to-event was 14 months. The patient did not have detectable visual field changes, but electroretinography (ERG) test revealed retinal toxicity. Vigabatrin treatment was discontinued. Medical history included premature birth (28 weeks), failure to thrive, cerebral palsy, patent ductus arteriosus, developmental delay, and chromosomal disorder. Concomitant medications were not reported.

FAERS #8479663v1
A 2-year-old female experienced vision loss. Vigabatrin total daily dose was 2000 mg and was used for the treatment of infantile spasms. Time-to-event was unknown. Retinal toxicity was confirmed by ERG. Vigabatrin treatment was discontinued. Medical history was not reported. Concomitant medications included ACTH and topiramate.

FAERS #9859918v1
A 4-year-old female experienced central and peripheral vision loss. Vigabatrin total daily dose was 3000 mg and was used for the treatment of CPS and tuberous sclerosis. Time-to-event was one year. A six-month follow-up OA described severe visual impairment, confirmed by fundoscopic exam. An ERG was not conducted as its findings were not going to result in therapy changes (benefit was greater than the risk). Vigabatrin treatment was continued. Medical history included tuberous sclerosis. Concomitant medications included phenobarbital and valproic acid.

FAERS #7110748v4
A 7-year-old female experienced a right homonymous hemianopsia with remaining function in the left visual field and ability to fix the vision. Vigabatrin total daily dose varied between 500 mg and 1200 mg. Time-to-event was 4 years. Vigabatrin treatment was discontinued. Medical history included a brain injury after a neonatal intracranial bleeding, severe cerebral paresis, and developmental disorder. Concomitant medications were not reported.

FAERS #8577841v2
A 7-year-old male experienced vision loss. Vigabatrin total daily dose was 500 mg and was used for the treatment of infantile spasms. Time-to-event was 21 months. Vision loss was confirmed by ERG, but further details were not reported. Vigabatrin treatment was to be discontinued. Medical history included ketogenic diet. Concomitant medications included lamotrigine 62.5 mg daily.

FAERS #9669961v2
A 14-year-old female developed gradual vision loss; light perception only. Vigabatrin total daily dose was 2500 mg and was used for the treatment of infantile spasms. Time-to-event was unknown. Diagnostic tests included MRI to rule out lesion and ERG (test results not provided). Vigabatrin treatment was continued. Medical history included tuberous sclerosis. Concomitant medications were not reported.

3.4.2 Labeled Event: Abnormal MRI (n=27)

[Patient age: range 4 months-6 years (mean 1.5 years; median 1 year)]

Vigabatrin is labeled for "MRI Abnormalities in Infants" in the Warnings and Precautions Section. In retrospective studies, postmarketing experience, and literature reports, MRI changes generally resolved with discontinuation of treatment.[3,4,5] In addition, some infants exhibit coincident motor abnormalities, but no causal relationship has been established.[6] In a few

patients, the lesion resolved despite continued use. Although clinical trial data and published literature provide evidence that brain MRI abnormalities are seen in infants treated with vigabatrin for infantile spasms, the potential for long-term clinical sequelae has not been adequately studied. We reviewed the event of abnormal MRI because of the inconclusive relationship between the MRI abnormalities and their clinical manifestations. The events reported in this pediatric case series were consistent with the known risk in the labeling. Below is a summary of the cases.

Twenty-seven unique cases reported the event of abnormal MRI. Seven cases reported hospitalization. Reported age ranged from 4 months to 6 years (mean 1.5 years; median 1 year). Vigabatrin total daily dose reported in 15 cases ranged from 750 mg to 2400 mg (mean 1300 mg; median 1000 mg) and was used for the treatment of infantile spasms (n=13), partial seizures (n=1), and seizures/epilepsy NOS (n=1). Time-to-event reported in 5 cases ranged from 91 days to 390 days (mean 228 days; median 180 days). Action taken with vigabatrin treatment was reported as ongoing (n=4), discontinued (n=12), or unknown (n=11).

Of the 27 cases reporting the event of abnormal MRI, 12 cases had insufficient MRI detail, medical history, or concomitant medications.

Six cases reported MRI signal changes consistent with the changes described in the vigabatrin labeling. Medical history included tuberous sclerosis (n=2), infantile spasms (n=5), global developmental delay (n=1), Aicardi's syndrome (n=1), Down syndrome (n=1), autism (n=1), and septo-optic dysplasia (n=1). Cases reported the concomitant use of at least one of the following medications: ACTH (n=2), levetiracetam (n=4), topiramate (n=3), zonisamide (n=2), lamotrigine (n=1), and valproic acid (n=1). Follow-up MRI results and the event outcome were not reported; however, we cannot rule out the role of vigabatrin.

Four cases were literature reports; *Aguilera-Albesa et al*.[6] described four cases that experienced central tegmental tract hyperintense signal on T2-weighted MRI. Vigabatrin (dose unknown) was used for the treatment of West syndrome. Three cases (ages 3, 4, and 6 months) exposed to vigabatrin experienced MRI changes after 3, 5, and 16 months, respectively. One case (age 4 months) experienced MRI changes prior to vigabatrin exposure. Medical history included cerebral palsy (n=2), left temporal atrophy (n=1), Cytomegalovirus infection (n=1), and hydrocephalus (n=1). Concomitant medications were not reported. This retrospective study of 17 patients demonstrated similar MRI changes among patients with West syndrome, regardless of vigabatrin exposure. The authors further concluded that the MRI changes represented a normal, physiological maturation-related process, possibly modified by additional endogenous or extraneous factors.

The remaining five cases reported a positive dechallenge after vigabatrin discontinuation (MRI changes and movement disorder in the first three cases and MRI changes in the last two cases). These five cases are described below.

FAERS #9144663v2

A 23-month-old female experienced movement disorder/chorea. An MRI revealed diffusion restriction in the thalamus bilaterally and decreased restriction with decreased

fractional anisotropy in dorsal pons. Vigabatrin total daily dose was 1250 mg and was used for the treatment of infantile spasms. Time-to-event was 11 months. Vigabatrin was discontinued and the event of movement disorder improved. Medical history included lissencephaly. Concomitant medications included zonisamide 75 mg twice daily and ACTH.

FAERS #11129042v2
A 25-month-old female experienced increasing tremors, dystonic movements, and encephalopathy. An MRI revealed changes in the basal ganglia of bilateral restricted diffusion and medial globus pallidus. Baseline MRI was normal (3 months prior to abnormal findings). Vigabatrin total daily dose was 800 mg and was used for the treatment of infantile spasms with intractable epilepsy. Time-to-event was 91 days. Vigabatrin treatment was discontinued and the events of tremor and dystonia improved. Medical history included bilateral open lip schizencephaly and severe developmental delay. Concomitant medications included levetiracetam 330 mg twice daily and clobazam 6.25 mg twice daily.

FAERS #10520705v2
A 3-year-old male experienced an abnormal MRI; signal described as bilateral caudate palidus and globes with restricted diffusion. Vigabatrin total daily dose was 1000 mg and was used for the treatment of CPS. Time-to-event was 760 days. Vigabatrin was discontinued and the follow-up MRI demonstrated full resolution of the abnormalities. Medical history included developmental delay, cerebellar loss, and congenital mitochondrial cytopathy. Concomitant medications included clobazam, rufinamide, and zonisamide.

FAERS #10287138v3
A 6-year-old female experienced involuntary movements and an abnormal MRI and EEG. An MRI revealed increased T2 signal at bilateral thalami; central degeneration plus dendrite nuclei. Vigabatrin total daily dose was 1500 mg and was used for the treatment of infantile spasms. Time-to-event was unknown. Vigabatrin was discontinued and the involuntary movements resolved. No further tests were performed. Medical history included infantile spasms and seizures NOS. Concomitant medications were not reported.

FAERS #9627275v1
Hsieh et al.[7] described an infant (age and sex unknown) experiencing an abnormal MRI; restricted diffusion in the bilateral brainstem, basal ganglia, and thalami. Vigabatrin total daily dose was unknown and was used for the treatment of infantile spasms. Time-to-event was unknown. Vigabatrin was discontinued and the follow-up MRI demonstrated full resolution of the abnormalities. Medical history included hypopigmented skin macules, cardiac rhabdomyomas, cortical tubers and subependymal nodules, and tuberous sclerosis. Concomitant medications were not reported.

3.4.3 Unlabeled Event: Renal Events (n=8)

[Patient age: range 7 months-8.7 years (mean 3.9 years; median 2.5 years)]

Vigabatrin is not labeled for renal events. We reviewed renal events because vigabatrin dose is adjusted in pediatric patients (≥10 years of age) with renal impairment. Below is a summary of the cases.

Eight cases reported the events of renal disorder (n=4), renal failure (n=3), or renal impairment (n=1). Six cases reported hospitalization and two cases reported death. Reported age ranged from 7 months to 8.7 years (mean 3.9 years; median 2.5 years). Vigabatrin total daily dose reported in 7 cases ranged from 124 mg to 2000 mg (mean 1050 mg; median 1000 mg) and was used for the treatment of infantile spasms (n=7). Time-to-event reported in one case was 510 days. None of the cases reported serum creatinine (SCr) levels. Action taken with vigabatrin treatment was reported as ongoing (n=6) or unknown (n=2).

Of the four cases reporting the event of renal disorder, one case reported a history of renal issues and three cases reported insufficient information. Medical history reported in one case included nephrolithiasis, renal issues, Leigh Syndrome, global developmental disorder, spastic cerebral palsy, and congenital cortical visual impairment. Concomitant medications reported in two cases included lamotrigine (n=1), levetiracetam (n=1), topiramate (n=1), and phenobarbital (n=1). The underlying disorders could have contributed to the event; however, we cannot rule out the role of vigabatrin.

Of the three cases reporting the event of renal failure, two cases reported multi-system organ failure, of which one resulted in death. Medical history reported in one case included Chiari type 1 malformation. Concomitant medications included topiramate (n=3) and phenobarbital (n=1). The underlying disorders could have contributed to the event; however, we cannot rule out the role of vigabatrin.

One case (8 year-old male) reported the event of renal impairment. Vigabatrin total daily dose was 1000 mg and was used for the treatment of infantile spasms. The patient was on vigabatrin therapy until death. Time-to-death was 1260 days. The patient's kidney function was reported as declining quickly six days prior to his death. He was not a candidate for kidney dialyses or transplant and his SCr was not monitored. Medical history included chronic kidney disease stage 4, hypertension, urinary sediment, anemia, bone marrow failure, Leigh syndrome, and developmental delay. Concomitant medications included levetiracetam, felbamate, and lamotrigine. The underlying disorders could have contributed to the event; however, we cannot rule out the role of vigabatrin. This case is also described in **Section 3.3.12.**

3.4.4 Unlabeled Event: Pancreatitis (n=5)

[Patient age: range 2.4 years-12 years (mean 4.9 years; median 3.6 years)]

Vigabatrin is not labeled for pancreatitis. Below is a summary of the cases.

Five cases reported the event of pancreatitis. All cases reported hospitalization. Reported age ranged from 2.4 years to 12 years (mean 4.9 years; median 3.6 year). Vigabatrin total daily dose reported in 6 cases ranged from 500 mg to 1600 mg (mean 1160 mg; median 1200 mg) and was used for the treatment of infantile spasms (n=4) and seizures/epilepsy NOS (n=1). Time-to-event reported in 4 cases ranged from 300 days to 720 days (mean=547 days; median=584 days). Amylase and lipase were reported in two cases. Action taken with vigabatrin treatment was reported as ongoing (n=1), discontinued (n=3), or unknown (n=1). None of the cases reported rechallenge.

Of the five cases reporting the event of pancreatitis, two cases provided no information on medical history and concomitant medications or contained insufficient information to assess causality.

Of the remaining three cases, two cases reported being on the ketogenic diet. The event of pancreatitis resolved upon discontinuation of ketogenic diet in one case and discontinuation of both vigabatrin and ketogenic diet in another case. One case reported the event resolved while continuing treatment with vigabatrin. Medical history included ketogenic diet (n=3), respiratory failure/distress (n=2), Miller-Deiker syndrome (n=1), severe developmental delay (n=1), failure to thrive (n=1), feeding intolerance (n=1), and small intestinal obstruction (n=1). Concomitant medications included levetiracetam (n=3, labeled for pancreatitis), topiramate (n=1, labeled for pancreatitis), rufinamide (n=1, unlabeled), phenobarbital (n=1, unlabeled), and clobazam (n=1, unlabeled). The ketogenic diet and concomitant medications could have contributed to the event; however, we cannot rule out the role of vigabatrin.[8]

4 DISCUSSION

Drug utilization data shows pediatric patients accounted for the majority of patients receiving a dispensed prescription for vigabatrin from mail-order pharmacies, August 2012 through July 2015. Among pediatric patients, over two-thirds of vigabatrin use was in children less than 6 years of age. This is consistent with the serious U.S. FAERS reports included in this review where the majority of cases involved children less than six years of age. This finding may be a reflection of vigabatrin approved indication for infantile spasms in infants 1 month to 2 years of age. The number of pediatric patients receiving a prescription for vigabatrin roughly doubled across all age groups over the examined time period. Neurologists were the top prescribing group, followed by pediatricians. No diagnosis data associated with the use of vigabatrin in pediatric patients were captured in our physician survey database during the examined study period.

We identified 1,001 serious U.S. FAERS pediatric reports with vigabatrin that were received from August 1, 2013 to July 31, 2015, including 154 cases reporting an outcome of death. The 154 cases reporting an outcome of death described 87 DECs. The majority of the serious reports

other than death described labeled adverse events. We identified and reviewed 222 U.S. FAERS pediatric cases, including 154 cases reporting an outcome of death and 68 cases reporting the events of special interest (received from August 21, 2009 to July 31, 2015). The events of special interest included blindness (unlabeled), renal events (unlabeled), pancreatitis (unlabeled), and abnormal MRI (labeled).

Vigabatrin is marketed under risk management plans, which can result in a greater surveillance of its adverse events. Most of our vigabatrin FAERS reports were received from a SHARE representative. The REMS for vigabatrin establishes several points of contact between the manufacturer and physicians, pharmacists and patients that do not ordinarily exist for the vast majority of marketed drugs without similar plans. These points of contact allow for much greater routine surveillance and reporting of adverse events and deaths than would otherwise be possible under usual surveillance practice. This is a plausible explanation for the number of cases with death as an outcome. The enhanced surveillance resulting from the risk management plans makes it much more likely that deaths, and adverse events in general, will be reported to FDA.

Death

Of the 154 U.S. FAERS pediatric cases reporting an outcome of death, most of the cases described disease progression, infection, respiratory insufficiency, and underlying congenital disorders, such as Aicardi's, Cockayne, Dandy-Walker, Miller-Diecker, Ohtahara, and Leigh syndrome, as possible contributory factors. The most frequently reported cause of death was unknown in 106 (69%) cases. In the majority of cases reporting a cause of death, the reported cause of death was respiratory in 24 (16%), cardiac in 10 (6%), and neurological in 10 (6%) cases. The reported cause of death is not unexpected in this patient population.[9,10] Clinical details surrounding death were not well-described or the cases contained insufficient information to assess causality.

Patients were generally younger, with 70 (45%) under 2 years of age, 61 (40%) between 2 and 6 years of age, 17 (11%) between 6 and 12 years of age, and 6 (4%) older than 12 years of age. The cases reported 71 (47%) males and 79 (53%) females. The prognosis for patients with infantile spasms is generally poor. Prognosis is dependent on the underlying cause, with the most common cause being neurological impairment.[11] It has been reported that approximately 33% of patients die before 3 years of age and 50% before 10 years of age.[12]

Vigabatrin total daily dose ranged from 150 mg to 6000 mg (mean 1438 mg; median 1200 mg) and the reported reason for use was infantile spasms, partial seizures, generalized seizures, seizures/epilepsy NOS, and tuberous sclerosis. For the reported reason for use of infantile spasms and tuberous sclerosis, the total daily dose ranged from 150mg to 6000 mg (mean 1334 mg; median 1000 mg). Recommended vigabatrin dosing is twice daily; however, cases reported once daily, and three times daily dosing. Fifteen cases reported weight information and vigabatrin was dosed appropriately. Time-to-death reported in 81 cases ranged from 2 days to 5.9 years (mean 1.6 years; median 1 year). Because of the risk of visual loss, vigabatrin should be discontinued in patients with infantile spasms within 2-4 weeks or sooner if treatment failure becomes obvious.

For the reported reason for use of partial, general, and seizures/epilepsy NOS, the total daily dose ranged from 450 mg to 4500 mg (mean 2000 mg; median 2002 mg). Recommended vigabatrin dosing is twice daily; however, cases reported once daily, three times daily, and four times daily dosing. Four cases reported weight information and vigabatrin was dosed appropriately. One case reported a total daily dose above 3000 mg. Doses above 3000 mg have not been shown to confer additional benefit and have been associated with increased incidence of adverse events. Time-to-death reported in 19 cases ranged from 1 day to 7.9 years (mean 2.4 years days; median 2.1 years). Because of the risk of visual loss, vigabatrin should be discontinued in patients with CPS who fail to show substantial clinical benefit within 3 months of initiation or sooner if treatment failure becomes obvious.

Events of Special Interest

Of the 68 U.S. FAERS pediatric cases reporting the events of special interest (blindness and abnormal MRI findings), all cases reported safety information consistent with the known risk in the labeling. Many cases lacked or provided limited information on patients' baseline clinical information, such as ophthalmologic tests, MRI details, laboratory tests, medical history, or concomitant medications; however, we cannot rule out the role of vigabatrin. In addition, although medical history, concomitant medication, or diet may have contributed to renal events and pancreatitis, we cannot rule out the role of vigabatrin.

Our evaluation of the 154 U.S. FAERS cases reporting an outcome of death and 68 cases reporting the events of special interest does not suggest any new or unexpected pediatric safety concerns with vigabatrin at this time.

DPV will continue postmarketing surveillance of all adverse events with the use of vigabatrin in pediatric patients.

5 CONCLUSION

We identified 1,001 serious U.S. FAERS pediatric reports with vigabatrin that were received from August 1, 2013 to July 31, 2015, including 154 cases reporting an outcome of death. The 154 cases reporting an outcome of death described 87 DECs. The majority of the serious reports other than death described labeled adverse events. We identified four events of special interest for further review (received from August 21, 2009 to July 31, 2015). The events of special interest included blindness (unlabeled), renal events (unlabeled), pancreatitis (unlabeled), and abnormal MRI (labeled).

The 154 cases reporting an outcome of death described disease progression, infection, respiratory insufficiency, or underlying congenital disorders. Clinical details surrounding death were not well-described or the cases contained insufficient information to assess causality. The 68 cases reporting the events of special interest (blindness and abnormal MRI) were consistent with the known risk in the labeling. Although medical history, concomitant medication, or diet may have contributed to renal events and pancreatitis, we cannot rule out the role of vigabatrin. Drug use data shows pediatric patients accounted for the majority of patients, largely patients less than 6 years of age.

Our evaluation of postmarketing adverse event reports does not suggest any new or unexpected pediatric safety concerns with vigabatrin at this time. DPV will continue postmarketing surveillance of all adverse events with the use of vigabatrin in pediatric patients.

6 RECOMMENDATIONS

DPV will continue postmarketing surveillance of all adverse events with the use of vigabatrin in pediatric patients.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Symphony Health Solutions' PHAST 2.0 Patient Monthly™

The Symphony Health Solutions' PHAST Patient Monthly is a syndicated view of U.S. retail and mail order pharmacy patient prescription activity, updated on a monthly basis at a projected national level. PHAST Patient monthly is based on the Symphony Health Solutions' longitudinal patient data source which captures adjudicated prescription claims across the United States across all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 10 billion prescriptions claims linked to over 220 million unique prescription patients with an average of 4.2 years of prescription drug history, of which approximately 140 million patients are linked to a diagnosis.

IMS, National Prescription Audit

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 80% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are available on-line for 72- rolling months with a lag of 1 month.

Encuity Research, LLC. TreatmentAnswers™

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient

activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

8.2 APPENDIX B. CHARACTERISTICS OF U.S. SERIOUS† PEDIATRIC REPORTS FOR VIGABATRIN, RECEIVED BY FDA FROM AUGUST 1, 2013 TO JULY 31, 2015 (N=847)

Age n=847	0 - < 1 month 1 month - <2 years 2- < 6 years 6- <12 years 12- < 17 years	1 412 262 120 52
Sex n=828	Male Female	419 409
Serious Outcome* n=934†	Death Life-threatening Hospitalized Disability Congenital anomaly Other serious	109 14 516 2 0 293
Reason for Use n=904†	Infantile spasms Partial seizures Generalized seizures Seizures/epilepsy NOS Tuberous Sclerosis	592 79 24 180 29

*Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.

†Reports may include more than one outcome and reason for use

8.3 APPENDIX C. 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 postmarketing 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 trade names 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.

8.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE U. S. PEDIATRIC FATAL CASES WITH VIGABATRIN (N=154)

SYSTEM ORGAN CLASS	FAERS CASE NUMBER	VERSION	MANUFACTURER CONTROL NUMBER
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (N=111)	9646157	1	US-LUNDBECK-DKLU1094705
	10026029	2	US-LUNDBECK-DKLU1072964
	10029017	1	US-LUNDBECK-DKLU1098306
	9517176	1	US-LUNDBECK-DKLU1093396
	11159202	1	US-LUNDBECK-DKLU1113261
	11245721	2	US-LUNDBECK-DKLU2001110
	11252672	2	US-LUNDBECK-DKLU2001170
	10883314	4	US-LUNDBECK-DKLU1109397
	10979439	1	US-LUNDBECK-DKLU1110664
	9993357	2	US-LUNDBECK-DKLU1098076
	10340682	1	US-LUNDBECK-DKLU1102039
	10073962	1	US-LUNDBECK-DKLU1099169
	10060779	2	US-LUNDBECK-DKLU1098854
	10434236	2	US-LUNDBECK-DKLU1103168
	11285584	1	US-LUNDBECK-DKLU2001539
	10711797	1	US-LUNDBECK-DKLU1107422
	10076706	3	US-LUNDBECK-DKLU1089871
	11051608	4	US-LUNDBECK-DKLU1111341
	10727650	3	US-LUNDBECK-DKLU1107704
	10228168	2	US-LUNDBECK-DKLU1100788
	10584664	1	US-LUNDBECK-DKLU1105423
	9790159	1	US-LUNDBECK-DKLU1096327
	11137459	1	US-LUNDBECK-DKLU1112817
	10541734	1	US-LUNDBECK-DKLU1104626
	10790741	1	US-LUNDBECK-DKLU1108507
	10922865	2	US-LUNDBECK-DKLU1109869
	11214072	2	US-LUNDBECK-DKLU2000513
	10155078	1	US-LUNDBECK-DKLU1099682
	10727905	2	US-LUNDBECK-DKLU1107747
	9841797	2	US-LUNDBECK-DKLU1096765
	9562547	1	US-LUNDBECK-DKLU1093873
	9831791	1	US-LUNDBECK-DKLU1096708
	9898786	3	US-LUNDBECK-DKLU1097314
	10995812	1	US-LUNDBECK-DKLU1110818
	10186025	4	US-LUNDBECK-DKLU1100046
	11281283	1	US-LUNDBECK-DKLU2001552
	9495736	2	US-LUNDBECK-DKLU1093315
	10397251	1	US-LUNDBECK-DKLU1102752
	9690263	1	US-LUNDBECK-DKLU1095240
	11057410	1	US-LUNDBECK-DKLU1111438
	11203834	1	US-LUNDBECK-DKLU2000350
	9602799	2	US-LUNDBECK-DKLU1094076
	10220665	2	US-LUNDBECK-DKLU1100592
	10446050	2	US-LUNDBECK-DKLU1103307
	9984547	1	US-LUNDBECK-DKLU1098004
	10332589	2	US-LUNDBECK-DKLU1094019
	9786178	1	US-LUNDBECK-DKLU1096269
	9889546	1	US-LUNDBECK-DKLU1097216
	10785257	3	US-LUNDBECK-DKLU1108398
	10060819	2	US-LUNDBECK-DKLU1098736
	11063833	1	US-LUNDBECK-DKLU1111532
	10056974	2	US-LUNDBECK-DKLU1068059
	10556130	2	US-LUNDBECK-DKLU1090049
	10521631	3	US-LUNDBECK-DKLU1097245
	9889443	2	US-LUNDBECK-DKLU1097164
	10756262	1	US-LUNDBECK-DKLU1108079
	10623146	3	US-LUNDBECK-DKLU1106028

	10737596	1	US-LUNDBECK-DKLU1107900
	9852905	3	US-LUNDBECK-DKLU1096463
	9871597	1	US-LUNDBECK-DKLU1097102
	10044126	1	US-LUNDBECK-DKLU1098477
	10557560	1	US-LUNDBECK-DKLU1104916
	10677730	1	US-LUNDBECK-DKLU1106850
	11100591	1	US-LUNDBECK-DKLU1112194
	9553887	2	US-LUNDBECK-DKLU1093790
	9627767	2	US-LUNDBECK-DKLU1092081
	9696332	2	US-LUNDBECK-DKLU1095419
	11091989	2	US-LUNDBECK-DKLU1111967
	11051888	1	US-LUNDBECK-DKLU1111372
	10550066	1	US-LUNDBECK-DKLU1104680
	11063845	2	US-LUNDBECK-DKLU1111653
	9786033	1	US-LUNDBECK-DKLU1096268
	9636089	1	US-LUNDBECK-DKLU1094370
	9814629	2	US-LUNDBECK-DKLU1096484
	10419542	1	US-LUNDBECK-DKLU1103011
	10474478	2	US-LUNDBECK-DKLU1103684
	9437476	1	US-LUNDBECK-DKLU1087296
	10477603	1	US-LUNDBECK-DKLU1103788
	10926990	2	US-LUNDBECK-DKLU1109811
	9476456	2	US-LUNDBECK-DKLU1093112
	9879759	1	US-LUNDBECK-DKLU1097064
	10255559	2	US-LUNDBECK-DKLU1096272
	11178270	1	US-LUNDBECK-DKLU1113303
	10730435	2	US-LUNDBECK-DKLU1107823
	10411075	3	US-LUNDBECK-DKLU1102840
	9617622	1	US-LUNDBECK-DKLU1094131
	9746193	3	US-LUNDBECK-DKLU1095891
	11117599	1	US-LUNDBECK-DKLU1112447
	11076807	1	US-LUNDBECK-DKLU1111726
	10121351	3	US-LUNDBECK-DKLU1099431
	10309141	2	US-LUNDBECK-DKLU1101794
	9617496	2	US-LUNDBECK-DKLU1094130
	11011324	2	US-LUNDBECK-DKLU1111027
	10794114	2	US-LUNDBECK-DKLU1108573
	10879963	1	US-LUNDBECK-DKLU1109271
	10555782	2	US-LUNDBECK-DKLU1104912
	11268085	1	US-LUNDBECK-DKLU2001352
	9542543	2	US-LUNDBECK-DKLU1093319
	10931066	1	US-LUNDBECK-DKLU1109979
	9494701	2	US-JNJFOC-20130816822
	10490449	1	US-LUNDBECK-DKLU1103900
	10585834	1	US-LUNDBECK-DKLU1105485
	10158558	1	US-LUNDBECK-DKLU1099708
	11010150	2	US-LUNDBECK-DKLU1110975
	10044978	1	US-LUNDBECK-DKLU1098513
	10358225	1	US-LUNDBECK-DKLU1102249
	11323699	1	US-LUNDBECK-DKLU2002008
	10701455	1	US-LUNDBECK-DKLU1107333
	11263096	1	US-LUNDBECK-DKLU2001230
	10464803	1	US-LUNDBECK-DKLU1103554
	11328117	1	US-LUNDBECK-DKLU2001475
RESPIRATORY, THORACIC, AND METABOLIC DISORDERS (N=30)	10299414	2	US-LUNDBECK-DKLU1101634
	10528135	3	US-LUNDBECK-DKLU1096345
	9562081	2	US-LUNDBECK-DKLU1093845
	9832617	2	US-LUNDBECK-DKLU1096669
	10769855	2	US-LUNDBECK-DKLU1107517
	9846915	2	US-LUNDBECK-DKLU1096921
	10251225	2	US-LUNDBECK-DKLU1101015
	10220665	2	US-LUNDBECK-DKLU1100592
	11042832	1	US-LUNDBECK-DKLU1111135

	10793810	2	US-LUNDBECK-DKLU1108503
	10056974	2	US-LUNDBECK-DKLU1068059
	10623522	3	US-LUNDBECK-DKLU1106033
	9907051	2	US-LUNDBECK-DKLU1097394
	9852905	3	US-LUNDBECK-DKLU1096463
	10484791	2	US-LUNDBECK-DKLU1103828
	9670007	2	US-LUNDBECK-DKLU1094835
	11116528	2	US-LUNDBECK-DKLU1112384
	10011086	2	US-LUNDBECK-DKLU1070505
	9841916	2	US-LUNDBECK-DKLU1096788
	10236126	3	US-LUNDBECK-DKLU1100885
	10255559	2	US-LUNDBECK-DKLU1096272
	10883314	4	US-LUNDBECK-DKLU1109397
	9907031	3	US-LUNDBECK-DKLU1097389
	10508889	2	US-LUNDBECK-DKLU1078331
	9818012	2	US-LUNDBECK-DKLU1096472
	9879476	2	US-LUNDBECK-DKLU1097217
	9650454	2	US-LUNDBECK-DKLU1094708
	10016558	2	US-LUNDBECK-DKLU1071799
	9781525	3	US-LUNDBECK-DKLU1096276
	10591433	3	US-LUNDBECK-DKLU1105487
NERVOUS SYSTEM DISORDERS (N=25)	10299414	2	US-LUNDBECK-DKLU1101634
	10287085	2	US-LUNDBECK-DKLU1101546
	10528135	3	US-LUNDBECK-DKLU1096345
	9832617	2	US-LUNDBECK-DKLU1096669
	10727905	2	US-LUNDBECK-DKLU1107747
	9898786	3	US-LUNDBECK-DKLU1097314
	10450133	2	US-LUNDBECK-DKLU1103417
	10186025	4	US-LUNDBECK-DKLU1100046
	9553763	2	US-LUNDBECK-DKLU1093796
	10220665	2	US-LUNDBECK-DKLU1100592
	9494701	2	US-JNJFOC-20130816822
	10446050	2	US-LUNDBECK-DKLU1103307
	10332589	2	US-LUNDBECK-DKLU1094019
	10056974	2	US-LUNDBECK-DKLU1068059
	9907051	2	US-LUNDBECK-DKLU1097394
	11116528	2	US-LUNDBECK-DKLU1112384
	10011086	2	US-LUNDBECK-DKLU1070505
	10526068	3	US-LUNDBECK-DKLU1104555
	10665955	1	US-LUNDBECK-DKLU1106725
	9476456	2	US-LUNDBECK-DKLU1093112
	9818012	2	US-LUNDBECK-DKLU1096472
	9500871	2	US-LUNDBECK-DKLU1083623
	10147515	3	US-LUNDBECK-DKLU1099569
	9757121	2	US-LUNDBECK-DKLU1084753
	10591433	3	US-LUNDBECK-DKLU1105487
INFECTIONS AND INFESTATIONS (N=20)	9832617	2	US-LUNDBECK-DKLU1096669
	9846915	2	US-LUNDBECK-DKLU1096921
	10186025	4	US-LUNDBECK-DKLU1100046
	10220665	2	US-LUNDBECK-DKLU1100592
	10446050	2	US-LUNDBECK-DKLU1103307
	10056974	2	US-LUNDBECK-DKLU1068059
	9638571	2	US-LUNDBECK-DKLU1094368
	10663144	2	US-LUNDBECK-DKLU1106576
	9670007	2	US-LUNDBECK-DKLU1094835
	9841916	2	US-LUNDBECK-DKLU1096788
	10716790	2	US-LUNDBECK-DKLU1107559
	9437476	1	US-LUNDBECK-DKLU1087296
	9476456	2	US-LUNDBECK-DKLU1093112
	10074125	2	US-LUNDBECK-DKLU1081498
	10508889	2	US-LUNDBECK-DKLU1078331
	9879476	2	US-LUNDBECK-DKLU1097217
	10121351	3	US-LUNDBECK-DKLU1099431

	10749027	3	US-LUNDBECK-DKLU1108073
	10309141	2	US-LUNDBECK-DKLU1101794
	9781525	3	US-LUNDBECK-DKLU1096276
CARDIAC DISORDERS (N=10)	10528135	3	US-LUNDBECK-DKLU1096345
	10387732	2	US-LUNDBECK-DKLU1102691
	10521631	3	US-LUNDBECK-DKLU1097245
	10484791	2	US-LUNDBECK-DKLU1103828
	11116528	2	US-LUNDBECK-DKLU1112384
	11245721	2	US-LUNDBECK-DKLU2001110
	9841916	2	US-LUNDBECK-DKLU1096788
	10790886	2	US-LUNDBECK-DKLU1108570
	10487925	2	US-LUNDBECK-DKLU1103887
	10926011	2	US-LUNDBECK-DKLU1109809
METABOLISM AND NUTRITION DISORDERS (N=6)	10186025	4	US-LUNDBECK-DKLU1100046
	10446050	2	US-LUNDBECK-DKLU1103307
	10521631	3	US-LUNDBECK-DKLU1097245
	10011086	2	US-LUNDBECK-DKLU1070505
	9841916	2	US-LUNDBECK-DKLU1096788
	9476456	2	US-LUNDBECK-DKLU1093112
CONGENITAL, FAMILIAL, AND GENETIC (N=4)	10663144	2	US-LUNDBECK-DKLU1106576
	9921972	2	US-LUNDBECK-DKLU1097610
	10526068	3	US-LUNDBECK-DKLU1104555
	10147515	3	US-LUNDBECK-DKLU1099569
GASTROINTESTINAL DISORDERS (N=4)	10446050	2	US-LUNDBECK-DKLU1103307
	10056974	2	US-LUNDBECK-DKLU1068059
	10526068	3	US-LUNDBECK-DKLU1104555
	10074125	2	US-LUNDBECK-DKLU1081498
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS (N=3)	10220665	2	US-LUNDBECK-DKLU1100592
	10332589	2	US-LUNDBECK-DKLU1094019
	10526068	3	US-LUNDBECK-DKLU1104555
VASCULAR DISORDERS (N=3)	10056974	2	US-LUNDBECK-DKLU1068059
	9841916	2	US-LUNDBECK-DKLU1096788
	9879476	2	US-LUNDBECK-DKLU1097217
INVESTIGATIONS (N=2)	10727905	2	US-LUNDBECK-DKLU1107747
	10186025	4	US-LUNDBECK-DKLU1100046
RENAL AND URINARY DISORDERS (N=1)	9617496	2	US-LUNDBECK-DKLU1094130

8.5 APPENDIX E. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE U.S. PEDIATRIC SERIOUS EVENTS OF SPECIAL INTEREST WITH VIGABATRIN (N=68)

ADVERSE EVENT	FAERS CASE NUMBER	VERSION	MANUFACTURER CONTROL NUMBER
BLINDNESS (N=28)	10525986	1	US-LUNDBECK-DKLU1104382
	10924167	1	US-LUNDBECK-DKLU1109769
	8784716	1	DKLU1084102
	8799832	2	DKLU1084492
	10770138	1	US-LUNDBECK-DKLU1108314
	9253147	3	US-LUNDBECK-DKLU1090356
	9914859	1	US-LUNDBECK-DKLU1097647
	10403347	1	US-LUNDBECK-DKLU1102832
	10202853	1	US-LUNDBECK-DKLU1100256
	9402105	1	US-LUNDBECK-DKLU1092349
	10063570	3	US-LUNDBECK-DKLU1098999
	10656480	2	US-LUNDBECK-DKLU1106456
	8479663	1	DKLU1077592
	8635753	1	DKLU1081493
	10425400	1	US-LUNDBECK-DKLU1103023
	10022882	2	US-LUNDBECK-DKLU1098239
	9156570	1	DKLU1088743
	9516290	1	US-LUNDBECK-DKLU1093405
	8560520	1	DKLU1079102
	9280954	1	US-LUNDBECK-DKLU1090721
	9859918	1	US-LUNDBECK-DKLU1096955
	8756002	2	DKLU1083739
	7110748	4	090824-0000932
	8577841	2	DKLU1079539
	9288093	1	US-LUNDBECK-DKLU1090840
	8014291	1	DKLU1071199
	9892603	1	US-LUNDBECK-DKLU1097310
	9669961	2	US-LUNDBECK-DKLU1094839
ABNORMAL MRI (N=2)	9627235	1	US-LUNDBECK-DKLU1084562
	9627236	1	US-LUNDBECK-DKLU1084563
	7577889	2	DKLU1064545
	10577457	2	US-LUNDBECK-DKLU1105230
	9301228	2	US-LUNDBECK-DKLU1090958
	11185910	1	US-LUNDBECK-DKLU2000252
	9627226	1	US-LUNDBECK-DKLU1084465
	9823314	2	US-LUNDBECK-DKLU1093316
	10186025	4	US-LUNDBECK-DKLU1100046
	9627546	2	US-LUNDBECK-DKLU1089454
	9816891	2	US-LUNDBECK-DKLU1096525
	9627592	2	US-LUNDBECK-DKLU1090152
	11111349	2	US-LUNDBECK-DKLU1112274
	11129042	2	US-LUNDBECK-DKLU1112715
	9605951	2	US-LUNDBECK-DKLU1078104
	9491744	2	US-LUNDBECK-DKLU1082093
	9627234	1	US-LUNDBECK-DKLU1084561
	9491782	1	US-LUNDBECK-DKLU1083197
	9144663	2	US-LUNDBECK-DKLU1088976
	9248591	2	US-LUNDBECK-DKLU1090167
	10520705	2	US-LUNDBECK-DKLU1097390
	10287138	3	US-LUNDBECK-DKLU1101350
	10197917	1	US-LUNDBECK-DKLU1100181
	10577441	1	US-LUNDBECK-DKLU1105232
	9491287	1	US-LUNDBECK-DKLU1078675
	9491288	1	US-LUNDBECK-DKLU1078676
	9627275	1	US-LUNDBECK-DKLU1084939
RENAL EVENTS (n=8)	9292239	1	DKLU1083115
	9983447	1	US-LUNDBECK-DKLU1097930

	10452968	2	US-LUNDBECK-DKLU1103493
	7971581	5	DKLU1069676
	8677103	1	DKLU1082684
	10265360	2	US-LUNDBECK-DKLU1101277
	9558387	2	US-LUNDBECK-DKLU1093962
	9617496	2	US-LUNDBECK-DKLU1094130
PANCREATITIS (n=5)	9196865	4	US-LUNDBECK-DKLU1089870
	8052977	1	DKLU1071753
	9144620	1	US-LUNDBECK-DKLU1088487
	9150025	1	DKLU1088487
	11236148	1	US-LUNDBECK-DKLU2001004

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