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 and Drug Utilization Review

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Product Name(s): Keppra (Levetiracetam)

Pediatric Labeling Approval Date: August 1, 2014

Application Type/Number:

NDA-021035	Keppra oral tablets
NDA-021505	Keppra oral solution
NDA-021872	Keppra injection for intravenous use
NDA-022285	Keppra extended-release (XR) oral tablets

Applicant/Sponsor: UBC Inc.

OSE RCM #: 2016-2894

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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 levetiracetam in pediatric patients.

Levetiracetam extended-release oral tablets were first approved in 2008, and the approved pediatric labeling is for adjunctive treatment of partial onset seizures in patients ≥12 years of age. Levetiracetam injection for intravenous use was first approved in 2006, and the approved pediatric labeling is for adjunctive treatment of partial onset seizures in patients ≥1 month of age, myoclonic seizures in patients ≥12 years of age, and primary generalized tonic-clonic seizures in patients ≥6 years of age.

In the outpatient setting, pediatric patients aged 0-16 years accounted for approximately 16% (25,280 patients) of total patients who received prescriptions for levetiracetam XR dispensed from U.S. outpatient retail pharmacies from August 2014 through December 2016. Of these pediatric patients, approximately half of the patients were ages 12-16 years. There was a small proportion of patients one year old and younger who received levetiracetam XR prescriptions; however, this use cannot be validated due to the lack of access to patient medical records. In the hospital setting, pediatric patients ages 0-16 years accounted for approximately 8% (79,000 patients) of total patients with a hospital discharge billing for injectable levetiracetam. Use of injectable levetiracetam was seen across all pediatric age groups. Please note that patient counts provided are not mutually exclusive as the patients are likely treated both inpatient and outpatient; therefore summing of patient populations will result in double counting of patients.

We identified 276 FAERS cases with levetiracetam in the U.S. pediatric population reporting a serious outcome, including 22 deaths. All 22 death cases reported alternative etiologies for the death or did not provide adequate information for causality assessment. Our evaluation of postmarketing adverse event reports does not suggest any new or unexpected pediatric safety concerns with levetiracetam at this time. The majority of reported drug event combinations were consistent with the known risks described in the labeling, or were disease-related or indication-related. We identified five cases related to the unlabeled events of cardiovascular adverse events, rhabdomyolysis, or encephalopathy with a possible causal association. No clear patterns or trends suggested a new safety signal associated with the other reported serious unlabeled adverse events in the pediatric case series.

We will continue routine pharmacovigilance for all pediatric adverse events associated with the use of levetiracetam, including cardiovascular adverse events, rhabdomyolysis, and encephalopathy as adverse events of interest in all patient populations.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Keppra (levetiracetam) is available in the following dosage forms:

- NDA-021035: oral tablets (250 mg, 500 mg, 750 mg, or 1000 mg)
- NDA-021505: oral solution (100 mg/ml)
- NDA-021872: injection for intravenous use (500 mg/5 ml)
- NDA-022285: extended-release (XR) oral tablets (500 mg, 750 mg)

Table 1 summarizes the U.S. approval history of Keppra (levetiracetam).

Table 1. U.S. Approval History of Keppra (Levetiracetam).

Date	Product Formulation*				Approved Indication(s)†
	PO tab	PO soln	IV soln	XR tab	
11/30/1999	X				• Adjunctive treatment of POS in patients ≥16 years of age
7/15/2003		X			
6/21/2005	X	X			• Adjunctive treatment of POS in patients ≥4 years of age
7/31/2006			X		• Adjunctive treatment of POS in patients ≥16 years of age
8/15/2006	X	X			• Adjunctive treatment of POS in patients ≥4 years of age • Adjunctive treatment of myoclonic seizures in patients ≥12 years of age
3/19/2007	X	X			• Adjunctive treatment of POS in patients ≥4 years of age • Adjunctive treatment of myoclonic seizures in patients ≥12 years of age • Adjunctive treatment of PGTCS in patients ≥6 years of age
9/12/2007			X		• Adjunctive treatment of POS in patients ≥16 years of age • Adjunctive treatment of myoclonic seizures in patients ≥16 years of age
5/16/2008			X		• Adjunctive treatment of POS in patients ≥16 years of age • Adjunctive treatment of myoclonic seizures in patients ≥16 years of age • Adjunctive treatment of PGTCS in patients ≥16 years of age
9/12/2008				X	• Adjunctive treatment of POS in patients ≥16 years of age
12/16/2011	X	X			• Adjunctive treatment of POS in patients ≥1 month of age • Adjunctive treatment of myoclonic seizures in patients ≥12 years of age • Adjunctive treatment of PGTCS in patients ≥6 years of age
8/1/2014				X	• Adjunctive treatment of POS in patients ≥12 years of age
10/30/2014			X		• Adjunctive treatment of POS in patients ≥1 month of age • Adjunctive treatment of myoclonic seizures in patients ≥12 years of age • Adjunctive treatment of PGTCS in patients ≥6 years of age

* PO = oral, soln = solution, IV = intravenous, XR = extended-release
† POS = partial onset seizures; PGTCS = primary generalized tonic-clonic seizures

OSE previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for levetiracetam in pediatric patients. This evaluation was triggered by the pediatric labeling changes on December 16, 2011, which extended the pediatric ages for the approved indications.[1] FDA presented this evaluation to the Pediatric Advisory Committee (PAC) on April 21, 2014. This evaluation did not identify any new safety concerns, and the PAC recommended return to standard, ongoing monitoring for adverse events with levetiracetam.

1.1.1 Pediatric Labeling Changes for Levetiracetam XR Oral Tablet

Levetiracetam XR oral tablets were first approved on September 12, 2008. The latest pediatric labeling changes occurred on August 1, 2014. FDA approved extending the indication for adjunctive treatment of POS from16 years of age to ≥12 years of age.

Safety and effectiveness in pediatric patients ≥12 years of age has been established based on pharmacokinetic (PK) data in adults and adolescents using levetiracetam XR and efficacy and safety data in controlled pediatric studies using immediate-release levetiracetam.

No new safety signals were observed in the PK studies for the latest pediatric labeling changes. Adverse events observed in these PK studies included somnolence, abnormal behavior, and a transient elevation in diastolic blood pressure.[2]

1.1.2 Pediatric Labeling Changes for Levetiracetam Injection for Intravenous Use

Levetiracetam injection for intravenous use was first approved on July 31, 2006. The latest pediatric labeling changes occurred on October 30, 2014. FDA approved extending the following indications:

- Adjunctive treatment of POS from ≥16 years of age to ≥1 month of age
- Adjunctive treatment of myoclonic seizures from ≥16 years of age to ≥12 years of age
- Adjunctive treatment of PGTCS from ≥16 years of age to ≥6 years of age

Safety and effectiveness in pediatric patients has been established based on PK data in adults and children using parenteral levetiracetam and efficacy and safety data in controlled pediatric studies using oral levetiracetam.

No new safety signals were observed in the PK studies for the latest pediatric labeling changes. Adverse events observed in these PK studies included convulsion, somnolence, dizziness, nausea, vomiting, hypotension, and skin reactions.[3]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current approved labels for levetiracetam (April 24, 2017) provide the following information excerpted from pertinent sections:[4-6]

WARNINGS AND PRECAUTIONS

Levetiracetam oral tablet, oral solution, XR oral tablet, and injection for IV use:

- **Behavioral Abnormalities and Psychotic Symptoms:** KEPPRA may cause behavioral abnormalities and psychotic symptoms. Patients treated with KEPPRA should be monitored for psychiatric signs and symptoms.
- **Somnolence and Fatigue:** KEPPRA may cause somnolence and fatigue. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on KEPPRA to gauge whether it adversely affects their ability to drive or operate machinery.
- **Anaphylaxis and Angioedema:** KEPPRA can cause anaphylaxis or angioedema after the first dose or at any time during treatment.
- **Serious Dermatological Reactions:** Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both pediatric and adult patients treated with KEPPRA.
- **Coordination Difficulties:** KEPPRA may cause coordination difficulties.
- **Withdrawal Seizures:** Antiepileptic drugs, including KEPPRA, should be withdrawn gradually to minimize the potential of increased seizure frequency.
- **Hematologic Abnormalities:** KEPPRA can cause hematologic abnormalities. Hematologic abnormalities occurred in clinical trials and included decreases in red blood cell (RBC) counts, hemoglobin, and hematocrit, and increases in eosinophil counts. Decreased white blood cell (WBC) and neutrophil counts also occurred in clinical trials. Cases of agranulocytosis have been reported in the postmarketing setting.
- **Seizure Control During Pregnancy:** Physiological changes may gradually decrease plasma levels of levetiracetam throughout pregnancy. This decrease is more pronounced during the third trimester. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period especially if the dose was changed during pregnancy.

Levetiracetam oral tablet, oral solution, and XR oral tablet only:

- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including KEPPRA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Levetiracetam oral tablet, oral solution, and injection for IV use only:

- **Increase in Blood Pressure:** In a randomized, placebo-controlled study in patients 1 month to <4 years of age, a significantly higher risk of increased diastolic blood pressure was observed in the KEPPRA-treated patients (17%), compared to the placebo-treated patients (2%). There was no overall difference in mean diastolic blood pressure between the treatment groups. The disparity between the KEPPRA and placebo treatment groups was not observed in the studies of older children or in adults.

ADVERSE REACTIONS

Levetiracetam oral tablet, oral solution, and injection for IV use only:

Most common adverse reactions (incidence ≥5% more than placebo) include:

- Adult patients: somnolence, asthenia, infection and dizziness
- Pediatric patients: fatigue, aggression, nasal congestion, decreased appetite, and irritability

Levetiracetam XR oral tablet only:

Most common adverse reactions (incidence ≥5% more than placebo) include: somnolence and irritability

OVERDOSAGE

Levetiracetam oral tablet, oral solution, XR oral tablet, and injection for IV use:

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans
The highest known dose of KEPPRA received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse reactions in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with KEPPRA overdoses in postmarketing use.

Management of Overdose
There is no specific antidote for overdose with KEPPRA. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with KEPPRA.

Hemodialysis
Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to FDA to conduct this analysis. Detailed database descriptions are provided in Appendix A.

2.2 DATA SOURCES USED

The QuintilesIMS, National Sales Perspectives™ was used to determine the settings of care where levetiracetam products were distributed based on the volume of drug products sold from the manufacturers to various U.S. distribution channels in 2016.

The QuintilesIMS, Total Patient Tracker™ database was used to obtain the nationally estimated number of patients who received a dispensed prescription for levetiracetam from U.S. outpatient retail pharmacies, stratified by formulation and by patient age (<1 year, 1 year, 2-5, 6-11, 12-16, 17 years and older) from August 1, 2014, through December 31, 2016, aggregated.

The QuintilesIMS Hospital Visit Analyzer database was used to determine the nationally estimated number of patients with an inpatient and outpatient hospital discharge billing for levetiracetam, stratified by formulation (oral includes IR/XR tablets and solution) and by patient age (<1 year, 1 year, 2-5, 6-11, 12-16, 17 years and older) from non-federal U.S. hospitals from August 1, 2014, through December 31, 2016, aggregated. Of note, given the limitations of this database, we are not able to provide breakdown of oral formulations, immediate-release, or extended-release.

2.3 RESULTS

2.3.1 Settings of Care

According to sales distribution data for 2016, 63% of levetiracetam bottles and vials were sold to U.S. non-retail settings of care (primarily non-federal hospitals), 33% to outpatient retail pharmacies, and 4% to mail-order/specialty pharmacy settings. Of the total market share, Oral levetiracetam, which includes immediate-release (IR) and extended-release (XR) tablets as well as oral solution, accounted for 62%, where approximately half were distributed to U.S. outpatient retail pharmacies. Injectable products accounted for 38% of the total market share, of which over 99% were distributed to non-retail (primarily non-federal hospitals) settings of care. Therefore, we focused on both hospital (inpatient and outpatient) and outpatient retail settings of care to examine the drug utilization trends for this review. Mail-order/specialty pharmacy and clinic data were not included in this review.

2.3.2 Outpatient Pharmacy Patient Level Data

Table 2. Nationally Estimated Number of Patients with Dispensed Prescriptions for Levetiracetam*, Stratified by Formulation and by Patient Age, from U.S. Outpatient Retail Pharmacies, August 1, 2014 - December 31, 2016

	August 1, 2014 - December 31, 2016	
	Patients (N)	***Share %***
Levetiracetam Total Patients	**2,378,146**	***100.0%***
0 - 16 years total	**363,968**	***15.3%***
17 years and older	**2,013,595**	***84.7%***
Levetiracetam Immediate Release (solution/tablet) Oral*	**2,282,064**	***96.0%***
0 - 16 years	**346,507**	***15.2%***
< 1 year	**27,932**	***8.1%***
1 year	**31,499**	***9.1%***
2 - 5 years	**102,201**	***29.5%***
6 - 11 years	**133,260**	***38.5%***
12 - 16 years	**108,789**	***31.4%***
17 years and older	**1,933,379**	***84.7%***
Age Unknown	**36,414**	***1.6%***
Levetiracetam Extended Release Oral	**154,983**	***6.5%***
0 - 16 years	**25,279**	***16.3%***
< 1 year	**547**	***2.2%***
1 year	**850**	***3.4%***
2 - 5 years	**4,933**	***19.5%***
6-11 years	**7,772**	***30.7%***
12 - 16 years	**13,094**	***51.8%***
17 years and older	**131,096**	***84.6%***
Age Unknown	**2,651**	***1.7%***
Levetiracetam Injection	**634**	***<0.1%***
0 - 16 years	**97**	***15.3%***
17 years and older	**531**	***83.8%***
Age Unknown	**10**	***1.6%***

Source: QuintilesIMS, Total Patient Tracker™. August 2014 - December 2016. Extracted April 2017.
File: TPT 2017-2894 levetiracetam BPCA April 2017.xls

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. Patients may have also received more than one drug product/formulation during the study period. Therefore, summing across patient age bands or drug products is not advisable and will result in overestimates of patient counts.

**Immediate release includes oral solution, tablet, and disintegrating tablet*

2.3.3 Inpatient and Outpatient Hospital Patient Level Data

Table 3. Nationally Estimated Number of Patients With an Inpatient or Outpatient Hospital Discharge Billing for Levetiracetam Stratified by Formulation and by Patient Age, from U.S. Non-Federal Hospitals, August 1, 2014 - December 31, 2016, Aggregated

	August 1, 2014 - December 31, 2016	
	Patients (N)	*Share %*
Levetiracetam Total Patients	**2,413,986**	***100.0%***
0 - 16 years total	**179,967**	***7.5%***
17 years and older	**2,235,533**	***92.6%***
Levetiracetam Oral*	**1,619,653**	***67.1%***
0 - 16 years	**99,564**	***6.1%***
< 1 year	**12,965**	***13.0%***
1 year	**8,735**	***8.8%***
2 - 5 years	**25,357**	***25.5%***
6 - 11 years	**27,220**	***27.3%***
12 - 16 years	**28,374**	***28.5%***
17 years and older	**1,520,818**	***93.9%***
Levetiracetam Injection	**1,009,962**	***41.84%***
0 - 16 years	**79,011**	***7.8%***
< 1 year	**13,650**	***17.3%***
1 year	**8,148**	***10.3%***
2 - 5 years	**20,438**	***25.9%***
6-11 years	**19,394**	***24.5%***
12 - 16 years	**18,615**	***23.6%***
17 years and older	**931,246**	***92.2%***
Levetiracetam Formulation Unspecified	**698,604**	***28.94%***
0 - 16 years	**63,321**	***9.1%***
17 years and older	**635,747**	***91.0%***

Source: QuintilesIMS, Hospital Visit Analyzer (HVA). Aug 2014 – Dec 2016. Extracted April-2017.
File: HVA 2016-2894 Levetiracetam BPCA April-2017.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. Patients may have also received more than one drug product/formulation during the study period. Therefore, summing across patient age bands or drug product/formulation is not advisable and will result in overestimates of patient counts.

**Oral levetiracetam includes immediate release (tablet, disintegrating tablets, oral solution) and extended release tablet.*

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 4. See Appendix B for a description of the FAERS database.

Table 4. FAERS Search Strategy

Date of Search	January 3, 2017
Time Period of Search	May 31, 2013* - December 31, 2016
Search Type	FBIS profile (or product manufacturer reporting summary) query FBIS quick query
Product Name(s)	Product name: Keppra, Keppra XR Product active ingredient: levetiracetam Active ingredient: levetiracetam
Search Parameters	All ages, outcomes, worldwide, MedDRA PTs (v19.1)

* May 31, 2013 is the date of FAERS data cutoff from the previous Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review presented at the April 2014 Pediatric Advisory Committee. U.S. approval dates of last pediatric labeling were August 1, 2014 for Keppra XR tablets and October 30, 2014 for Keppra IV solution.

We identified all U.S. pediatric FAERS reports of levetiracetam with a serious outcome received from May 31, 2013, to December 31, 2016. Serious outcomes per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. We screened all reported drug event combinations (DECs) during this timeframe for serious unlabeled events with levetiracetam. 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 reports received from May 31, 2013, to December 31, 2016, to capture adverse events that are considered rare, serious, and associated with a high drug-attributable risk. OSE created the DME list for working purposes; it has no regulatory significance. See Appendix C for a list of OSE's DMEs.

Furthermore, we used the Empirica Signal database to perform data mining and disproportionality analysis on all reported DECs for levetiracetam since product approval for all pediatric and adult FAERS reports. Data mining and disproportionality analysis identifies patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases (e.g., FAERS). Data mining complements our traditional signal detection approaches, as described above, 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 D for a description of data mining of FAERS using Empirica Signal.

This review focuses on deaths and serious unlabeled events of interest, identified in our data analysis described above, in the U.S. pediatric population from May 31, 2013, to December 31, 2016. We did not identify any additional events of interest with levetiracetam in the U.S. pediatric population in the other timeframes analyzed for this review.

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Our FAERS search retrieved 13,049 total reports for levetiracetam in all ages and countries from May 31, 2013, to December 31, 2016. Table 5 summarizes the total number of FAERS reports stratified by age and outcome.

Table 5. Total Adult and Pediatric FAERS Reports* From May 31, 2013, to December 31, 2016, With Levetiracetam (Total n=13,049)

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	6,194 (2,497)	5,397 (1,828)	629 (269)
Pediatrics (0 - <17 years)	1,505 (691)	**1,246 (470)‡**	86 (28)

* 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.

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 470 U.S. pediatric reports with levetiracetam reporting a serious outcome from May 31, 2013, to December 31, 2016 (see Table 5). Our pediatric case series included 276 cases, including 22 deaths, after excluding duplicate reports (n=173), transplacental exposure reports (n=19), and miscoded age reports (n=2).

3.2.3 Characteristics of Pediatric Case Series

Appendix E lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 6 summarizes the 276 FAERS cases in U.S. pediatric patients with levetiracetam reporting a serious outcome received by FDA from May 31, 2013, to December 31, 2016.

Table 6. Characteristics of U.S. Pediatric Case Series With Levetiracetam, Received by FDA From May 31, 2013, to December 31, 2016 (N=276)		
Age	0 - < 1 month	13
	1 month - <2 years	36
	2- < 6 years	84
	6- <12 years	78
	12- < 17 years	63
	Unknown pediatric	2
Sex	Male	129
	Female	134
	Unknown	13
Report Year	2013 (36), 2014 (62), 2015 (91), 2016 (87)	
Reported Reason for Use*	Seizures/epilepsy	201
	Unknown	16
	Neonatal seizures	12
	Partial seizures	10
	Status epilepticus	9
	Generalized seizures	8
	Seizure prophylaxis	6
	Infantile spasms	5
	Absence seizures	3
	Lennox-Gastaut syndrome	2
	Complex febrile seizures	1
	Dravet syndrome	1
	Juvenile myoclonic epilepsy	1
	"Shaking/spacing out"	1
Serious Outcome†	Death	22
	Life-threatening	20
	Hospitalized	85
	Disability	3
	Congenital anomaly	0
	Required Intervention	0
	Other serious	200

* Seizures/epilepsy includes: seizures, convulsions, and epilepsy. Partial seizures includes: partial seizures, complex partial seizures, frontal lobe seizures, temporal lobe seizures, and benign rolandic epilepsy. Generalized seizures includes: generalized tonic-clonic seizures and idiopathic generalized epilepsy.

† 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.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=22)

We identified 22 cases with levetiracetam reporting death as an outcome in the pediatric population. All 22 cases did not provide evidence of a causal association with levetiracetam. All 22 cases reported alternative etiologies for the death or did not provide adequate information for causality assessment. Most cases (18 of 22) reported death secondary to seizure, sudden unexpected death in epilepsy (SUDEP), or complications from hypoxic ischemic encephalopathy. The remaining four cases reported death secondary to respiratory failure or meningoencephalitis. More than half of the cases (12 of 22) also reported use of other concomitant antiepileptic drugs (AEDs). The cases are described below.

3.3.1 Seizure, SUDEP, or Complications from Hypoxic Ischemic Encephalopathy (n=18)

- FAERS #10930623v1: a 3-year-old male died secondary to seizure. The patient had received levetiracetam with several concomitant AEDs in the past, and the reporter inquired about the use of medicinal cannabis sativa because the AEDs were ineffective.
- FAERS #9604661v1, 9554651v2: a literature article[7] reported two pediatric patients (5-month-old female and 11-month-old male) died while receiving levetiracetam with several concomitant AEDs and therapeutic hypothermia for refractory status epilepticus. Both patients had a poor prognosis and were transitioned to comfort care.
- FAERS #10280172v1, 10280183v1: a literature article[8] reported two pediatric patients of unknown age (< 18 years old) died while receiving intravenous levetiracetam for seizures. This retrospective study reported "two patients died because of continued seizure activity on three anticonvulsants" and did not provide any patient specific details for these two cases.
- FAERS #9587733v3: an 8-year-old male died secondary to SUDEP. The patient had a history of intractable convulsive epilepsy and received levetiracetam with clobazam.
- FAERS #12536849v1: a literature article[9] reported an 11-year-old male died secondary to SUDEP. The patient had a history of Lennox-Gastaut syndrome and received levetiracetam with several concomitant AEDs.
- FAERS #12241983v1: a literature article[10] reported a 12-year-old male died secondary to SUDEP. The patient had a history of Lennox-Gastaut syndrome, infantile spasms, and meningoencephalitis and received levetiracetam with several concomitant AEDs.
- FAERS # 11610875v1: an 8-day-old female died while receiving levetiracetam with several concomitant AEDs for seizures in neonatal hypoxic ischemic encephalopathy. The patient had a poor prognosis and was transitioned to comfort care.
- FAERS #10957787v1: a literature article[11] reported a 9-month-old female died secondary to complications of influenza A-associated acute necrotizing encephalopathy and hypoxic ischemic encephalopathy. The patient presented with symptoms of pneumonia and developed seizures and subsequently received levetiracetam. The patient was diagnosed with influenza A-associated acute necrotizing encephalopathy and hypoxic ischemic encephalopathy. The patient's status progressively worsened and she died secondary to complications, including cardiac arrest with pulseless electrical activity, disseminated intravascular coagulation, and gastrointestinal and pulmonary hemorrhages.

- FAERS #13025491v1, 13025492v1, 13025493v1, 13025494v1, 13025499v1, 13025500v1, 13025541v1, 13025542v1: a literature article[12] reported eight neonates who died while receiving levetiracetam for seizures in neonatal hypoxic ischemic encephalopathy. This retrospective study reported 8 of 32 neonates treated with levetiracetam died and did not provide any patient specific details for these 8 cases.

3.3.2 Respiratory Failure or Meningoencephalitis (n=4)

- FAERS #11992572v1: a literature article[13] reported a 7-month-old male infant died secondary to respiratory failure after developing cerebral atrophy and subdural hematoma. The patient had a medical history of Pierson's syndrome and developed a catheter-associated thrombus and was placed on enoxaparin. The patient later developed cerebral atrophy, subdural hematoma, seizures, and status epilepticus and subsequently received levetiracetam with several concomitant AEDs, and transitioned to comfort care.
- FAERS #11102056v1: a literature article[14] reported a 32-month-old female died secondary to respiratory failure and disease progression from mutations in the polymerase gamma (POLG) gene of mitochondria. The patient developed seizures and status epilepticus and received levetiracetam with several concomitant AEDs.
- FAERS #11138725v1: a literature article[15] reported a 9-week-old male died secondary to respiratory illness while receiving levetiracetam with several concomitant AEDs and ketogenic diet for refractory status epilepticus.
- FAERS #10785131v1: a literature article[16] reported a 4-year-old male died secondary to meningoencephalitis after exposure to *Naegleria fowleri* in tap water from a treated public drinking water system. The patient was hospitalized for meningitis symptoms and was initiated on levetiracetam for "repeat staring spells, which were suggestive of seizures." The patient's status progressively worsened and died secondary to the meningoencephalitis.

3.4 SUMMARY OF ALL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=276)

We identified 276 FAERS cases with levetiracetam in the U.S. pediatric population reporting a serious outcome including the 22 death cases described above, with 351 DECs. 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. These adverse events are adequately described in the labeling, including several in Warnings and Precautions. Labeled DECs reported in ≥ 5 cases included:

- behavioral abnormalities and psychotic symptoms
- somnolence and fatigue
- gastrointestinal adverse events
- dermatological and allergic reactions
- movement disorders
- sleep disorders
- coordination difficulties or dizziness
- hematologic abnormalities
- suicidal behavior and ideation

Several unlabeled DECs were disease-related or indication-related. Unlabeled DECs related to the patient's underlying disease or indication for use reported in ≥ 5 cases included:

- seizures
- drug ineffective, condition aggravated
- product substitution issue, product use issue, product quality issue
- off label use, drug administered to patient of inappropriate age

The cases reporting ineffective drug and product issues primarily reported seizures with the use of levetiracetam. Several of these cases reported ineffective seizure control with the use of generic levetiracetam, and requested the use of brand Keppra for insurance coverage. We did not identify a trend with any specific levetiracetam products, lot numbers, or manufacturers associated with these DECs. Several cases also reported refractory seizures requiring the use of concomitant AEDs that were also ineffective for seizure control.

We identified four events of interest in the pediatric population with all levetiracetam formulations that are serious unlabeled DECs. These events include cardiovascular adverse events, rhabdomyolysis, encephalopathy, and neurophysiologic abnormalities. Our review focuses on these events of interest with levetiracetam in the U.S. pediatric population. No clear patterns or trends suggested a new safety signal associated with the other reported serious unlabeled adverse events in the pediatric case series.

We did not identify any additional events of interest specific to the extended-release or intravenous formulations of levetiracetam. Most events were consistent with the known risks described in the labeling, or were disease or indication related.

We identified 45 pediatric cases in unlabeled patient populations with levetiracetam reporting a serious outcome. We did not identify any additional events of interest specific to use of levetiracetam in these unlabeled patient populations. Most events were consistent with the known risks described in the labeling, or were disease or indication related. These 45 cases included:

- neonatal seizures (12)
- status epilepticus (9)
- seizure prophylaxis (6)
- infantile spasms (5)
- absence seizure (3)
- extended-release tablet in <12 years of age (3)
- generalized tonic-clonic seizures <6 years of age (2)
- Lennox-Gastaut Syndrome (2)
- Complex febrile seizures (1)
- Dravet syndrome (1)
- "shaking and spacing out" episodes (1)

3.4.1 Serious unlabeled DECs

We identified seven cases reporting seven serious unlabeled DECs of interest with levetiracetam in the pediatric population.

- Two cases (FAERS # 11549994v2, FAERS #10453143v4) reported cardiorespiratory failure or cardiac arrest after an intentional overdose of levetiracetam with other medications.
- One case (FAERS #10472342v1) reported hypotension after an unintentional overdose of levetiracetam.
- One case (FAERS #10884951v1) reported increased premature ventricular contractions (PVCs) in a neonate with pre-existing PVCs.
- One case (FAERS #13038769v1) reported rhabdomyolysis after receiving levetiracetam for tonic-clonic seizures.
- One case (FAERS #9494308v1) reported encephalopathy in a patient presenting with renal failure and metabolic acidosis on levetiracetam.
- One case (FAERS # 10772415v1) reported neurophysiologic abnormalities while receiving levetiracetam during craniotomy and tumor resection.

All seven cases reported evidence of a possible causal association with levetiracetam. However, many cases also reported other factors affecting the causality assessment. The cases are described below.

CARDIOVASCULAR ADVERSE EVENTS (N=4)

FAERS # 11549994v2, MCN: US-TEVA-596583USA, 2015: a literature article[17] reported a 16-year-old male developed lactic acidosis and cardiorespiratory failure after an intentional overdose of unknown amounts of multiple medications, including levetiracetam, metformin, and paroxetine. Medical history included depression. The patient presented unconscious with serum pH 7.13 [normal 7.35-7.45] and lactate 20.3 mmol/L [normal 0.5-2 mmol/L]. The patient received normal saline with sodium bicarbonate for lactic acidosis, was intubated for altered mental status, and received vasopressors for hypotension. On day 2, the patient's condition deteriorated and he developed cardiorespiratory failure and was placed on extracorporeal membrane oxygenation (ECMO) and hemodialysis. After 6 days of ECMO treatment, the patient was weaned from treatment and eventually had a full neurologic recovery.

Reviewer comment: *this case provides evidence of a possible causal association of lactic acidosis and cardiorespiratory failure with levetiracetam overdose because of the plausible temporal relationship. However, the concomitant ingestion of metformin and paroxetine provide a more likely alternative etiology. Metformin has been associated with lactic acidosis with hypotension, respiratory depression, and bradyarrhythmias. Paroxetine has been associated with hypotension, ventricular dysrhythmias, and bradycardia.*

FAERS #10453143v4, MCN: US-TEVA-508022USA, 2014: a literature article[18] reported a 16-year-old female developed cardiac arrest after an intentional overdose of levetiracetam (unknown amount), lacosamide 4.5 g, and cyclobenzaprine 120 mg. Medical history included seizure disorder, depression, three prior suicide attempts, and medication non-compliance. The patient presented with pulseless ventricular tachycardia, received defibrillation, and converted to sinus tachycardia. The patient then developed tonic-clonic seizure and received diazepam. The patient's condition deteriorated and she developed respiratory depression requiring intubation, asystole requiring epinephrine and atropine with cardiopulmonary resuscitation, possible sodium channel blockade requiring sodium bicarbonate, and QRS widening. Urine screen was positive for opiates. Approximately 9 hours after initial presentation, the serum lacosamide level was elevated, and serum levetiracetam and cyclobenzaprine levels were within the therapeutic range. On day 2, the patient was extubated, and on day 5, she returned to her neurologic baseline without any deficits and was medically cleared.

Reviewer comment: *this case provides evidence of a possible causal association of cardiac arrest with levetiracetam overdose because of the plausible temporal relationship. However, the concomitant ingestion of lacosamide and cyclobenzaprine provide a more likely alternative etiology because lacosamide has been associated with cardiac toxicity, and both of these medications are sodium channel blockers, which may affect cardiac conduction. In addition, the patient had a positive urine screen for opiates; opioid-induced respiratory arrest with hypoxia and acidosis may present similarly.*

FAERS #10472342v1, MCN: 2014PRN00023, 2014: a literature article[19] reported a 6-year-old male developed altered mental status and hypotension after an unintentional overdose of levetiracetam 10.5 g. Medical history included cerebral palsy, and concomitant medications were not reported. The patient's parent unintentionally administered 3.5 oz of levetiracetam 100 mg/ml oral solution via jejunostomy tube. Three hours post-ingestion, the patient presented with altered mental status, lethargy, and decreased gag reflex. The patient began to waken approximately 8 hours post-ingestion and mental status cleared throughout the day. The patient also developed hypotension with lowest measured blood pressure of 80/38 mmHg, managed with intravenous fluids. Approximately 24 hours post-ingestion, the patient was discharged home.

Reviewer comment: *this case provides evidence of a possible causal association of hypotension with levetiracetam because of the plausible temporal relationship and positive dechallenge after levetiracetam ingestion. However, the case lacks information regarding concomitant medications.*

FAERS #10884951v1, Direct report, 2015: a 3-day-old female developed increased premature ventricular contractions (PVCs) while receiving intravenous levetiracetam in a study for new-onset neonatal seizures secondary to hypoglycemia. Concomitant medications included acyclovir, ampicillin, and cefotaxime. The patient developed PVCs

prior to the first levetiracetam infusion. PVCs were observed between the first and second loading dose of levetiracetam, and appeared to increase in frequency during the third levetiracetam infusion. During the levetiracetam maintenance infusion, the patient began having PVCs at a frequency of approximately 1 every 10 seconds. There were no clinical changes associated with the PVCs observed on the monitor. Levetiracetam was discontinued and changed to phenobarbital and the PVCs resolved. Additional findings included MRI of head showing venous infarct and normal electrolyte panel.

Reviewer comment: *this case provides evidence of a possible causal association of increased PVCs with levetiracetam because of the plausible temporal relationship and positive dechallenge after levetiracetam discontinuation. However, the patient had pre-existing PVCs prior to receiving the first dose of levetiracetam.*

RHABDOMYOLYSIS (N=1)

FAERS #13038769v1, MCN: US-ACCORD-046568, 2016: a literature article[20] reported a 16-year-old male experienced rhabdomyolysis while receiving levetiracetam for new onset seizures. Medical history was unremarkable. The patient was hospitalized after developing two generalized tonic-clonic seizures. The first seizure occurring at school lasted for 2 minutes and the second seizure occurring in the emergency department lasted for 2.5 minutes. There was no reported fall or other trauma to the patient before or during the seizure. The patient was started on lorazepam and intravenous levetiracetam [unknown dose], and a normal saline bolus followed by maintenance fluid, and during hospitalization was started on levetiracetam 750 mg PO BID. Laboratory values on admission included serum bicarbonate 18 mmol/L [normal 21-29 mmol/L], normal serum electrolytes and creatinine, and negative urinalysis and drug screen. The following day, the patient developed back pain. Laboratory values included creatine kinase (CK) 565 U/L [normal 94-499 U/L], serum creatinine (SCr) 2.2 mg/dL [normal 0.5-1.2 mg/dL], and urinalysis positive for myoglobin and negative for protein, red blood cells, white blood cells, and bacteria. Potassium was omitted from the maintenance fluids and the rate was increased to 200 ml/h for hydration. The patient's back pain worsened and spread to other locations and required narcotics for pain control. On day 4, CK was 15,111 U/L and SCr "remained elevated with only mild fluctuations." On day 5, levetiracetam was discontinued and changed to divalproex sodium. By day 7, the patient's back pain completely resolved and SCr "normalized," and by day 10, CK "normalized." The patient was discharged on divalproex sodium and subsequent SCr and CK laboratories were normal.

Reviewer comment: *this case provides evidence of a possible causal association of rhabdomyolysis with levetiracetam because of the plausible temporal relationship and positive dechallenge after levetiracetam discontinuation. However, the two generalized tonic-clonic seizures one day prior to the event may provide an alternative etiology; tonic-clonic seizures may cause CK elevation and are a nontraumatic exertional cause of rhabdomyolysis.*

ENCEPHALOPATHY (N=1)

FAERS #9494308v1, MCN: LEVE20130007, 2013: a literature article[21] reported a 12-year-old female developed encephalopathy with opsoclonus and triphasic waves on electroencephalogram (EEG) while receiving levetiracetam (unknown dose and duration) for epilepsy. Medical history included Chiari II malformation, repaired myelomeningocele, shunted hydrocephalus, and renal tubular acidosis. Concomitant medications were not reported. The patient was hospitalized for acute renal failure, metabolic acidosis, respiratory distress, and confusion. The patient received treatment for metabolic abnormalities and respiratory failure and had continued renal impairment. Within a few hours, the patient became increasingly somnolent, tremulous and encephalopathic. Neurologic findings included continuous, random conjugate jerky eye movements in all directions of gaze (opsoclonus) and chin quivering with occasional multifocal twitches of lower face muscles. EEG showed diffuse delta with continuous runs of periodic frontally predominant sharp waves consistent with triphasic waves. The patient was treated with lorazepam and fosphenytoin without resolution of symptoms. The plasma level of levetiracetam was 112 mcg/ml (reported therapeutic range 5–60 mcg/ml) and the dose of levetiracetam was adjusted for creatinine clearance. Continuous EEG over several days showed persistent triphasic waves. Other causes of metabolic encephalopathy were excluded. Levetiracetam was discontinued and the patient was started on valproate. Over the next 4-5 days abnormal eye movements resolved, and the patient gradually returned to baseline. Follow-up EEG showed resolution of triphasic waves.

Reviewer comment: *this case provides evidence of a possible causal association of encephalopathy with levetiracetam because of the plausible temporal relationship and positive dechallenge after levetiracetam discontinuation. However, the case reports a supratherapeutic level of levetiracetam and other factors that may affect the causality assessment (acute renal failure, metabolic acidosis, respiratory distress) and lacks information regarding concomitant medications.*

NEUROPHYSIOLOGIC ABNORMALITIES (N=1)

FAERS # 10772415v1, MCN: US-ACCORD-028505, 2015: a literature article[22] reported a 12-year-old female developed transient loss of transcranial electrical motor-evoked potential (tceMEP) signals while receiving intravenous levetiracetam 10 mg/kg for seizure prophylaxis during craniotomy and tumor resection. Medical history included fibrillary astrocytoma of the right temporal lobe and persistent seizures. Concomitant home medications included topiramate and clorazepate. Concomitant hospital medications included midazolam, propofol, remifentanil, and inadvertent administration of succinylcholine. Baseline tceMEPs were normal at the start of the procedure. Ten minutes after initiating levetiracetam infusion (10 mg/kg over 30 minutes) during surgery, an abrupt, global decrease in tceMEP amplitude was observed, despite near-baseline vital signs, no other recent medication boluses, and minimal intracranial dissection (i.e., surgical trauma) at that point. The levetiracetam infusion was stopped,

and 3 minutes later, the tceMEP amplitude returned to baseline. TceMEPs remained stable throughout the remainder of surgery. After completion of surgery, the same levetiracetam infusion was resumed, and again a similar global decrease in tceMEP amplitude was observed, which resolved several minutes after cessation of the levetiracetam infusion. The patient experienced a full recovery after surgery.

Reviewer comment: *this case provides evidence of a probable causal association of transient loss of transcranial electrical motor-evoked potential (tceMEP) signals with levetiracetam because of the plausible temporal relationship, positive dechallenge after levetiracetam discontinuation, and positive rechallenge after levetiracetam restart. This phenomenon may have implications in surgical procedures using this electrophysiologic monitoring technique in combination with levetiracetam and concurrent general anesthetics (e.g., suboptimal resection of tumor due to misinterpretation of MEP changes).*

4 DISCUSSION

In the outpatient setting, pediatric patients ages 0-16 years accounted for approximately 16% (25,280 patients) of total patients who received a prescription for levetiracetam XR from U.S. outpatient retail pharmacies from August 2014 through December 2016. Of these pediatric patients, approximately half were ages 12-16 years. There was a small proportion of patients one year old and younger who received levetiracetam XR prescriptions; however, this use could not be validated due to the lack of access to patient medical records. In the hospital setting, pediatric patients aged 0-16 years accounted for approximately 8% (79,000 patients) of total patients with a hospital discharge billing for injectable levetiracetam. However, these data may underrepresent pediatric utilization of levetiracetam in the hospital setting, as the data sources do not capture data from pediatric standalone hospitals. Use of injectable levetiracetam was seen across all pediatric age groups. Please note that patient counts provided are not mutually exclusive as the patients are likely treated both inpatient and outpatient and with multiple formulations over time; therefore summing of patient populations will result in double counting of patients.

Our review of the 276 FAERS cases with levetiracetam in the U.S. pediatric population demonstrated the majority of cases (263 of 276) were reported in pediatric patients ≥ 1 month of age. The most commonly reported reason for use was unspecified seizures/epilepsy (201), and all reported reasons for use were related to seizures and epilepsy.

Our review of the DECs reported in the 276 FAERS cases with levetiracetam in the U.S. pediatric population, including unlabeled patient populations, 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. The majority of labeled DECs were related to behavioral abnormalities and psychotic symptoms, somnolence and fatigue, gastrointestinal adverse events, dermatological and allergic reactions, movement disorders, sleep disorders, coordination difficulties or dizziness, hematologic abnormalities, or suicidal behavior and ideation. These adverse events are adequately described in the labeling, including several in Warnings and Precautions.

Several unlabeled DECs were disease-related or indication-related, including seizures, drug ineffective, condition aggravated, product substitution issue, product use issue, product quality issue, off label use, and drug administered to patient of inappropriate age. The cases reporting ineffective drug and product issues primarily reported seizures with the use of levetiracetam. Seizures are expected in this patient population with epilepsy, therefore the events of seizure reported in this pediatric case series are consistent with treatment of the disease state. We did not identify a trend with any specific levetiracetam products, lot numbers, or manufacturers associated with these DECs.

We identified 22 FAERS cases reporting death as an outcome with levetiracetam in the U.S. pediatric population; however, all 22 cases did not provide evidence of a causal association with levetiracetam. All 22 cases reported alternative etiologies for the death or did not provide adequate information for causality assessment. Most cases (18 of 22) reported death secondary to seizure, SUDEP, or complications from hypoxic ischemic encephalopathy. The remaining four cases reported death secondary to respiratory failure or meningoencephalitis. More than half of the cases (12 of 22) also reported use of other concomitant AEDs, which also affects the causality assessment. In addition, children with epilepsy have an overall mortality rate of 228 per 100,000 person-years, 5 to 10 times greater than the age-matched death rate in the general population.[23] The incidence of SUDEP in children with epilepsy is approximately 0.22/1,000 patient-years.[24]

We identified four FAERS cases reporting the unlabeled events of cardiovascular adverse events, including cardiac arrest, cardiorespiratory failure, hypotension, and increased premature ventricular contractions. Three cases provided reasonable evidence of a possible causal association with levetiracetam because of the plausible temporal relationship. These three cases reported adverse events (cardiac arrest, cardiorespiratory failure, or hypotension) occurring after an overdose of levetiracetam. However, two of these three cases also reported ingestion of concomitant medications (metformin and paroxetine; lacosamide and cyclobenzaprine) that may provide an alternative etiology for the cardiac adverse event. Cardiac adverse events, including bradycardia and hypotension, have also been reported with levetiracetam overdose in the adult population.[25] In addition, levetiracetam partially inhibits N-type calcium currents in neuronal cells *in vitro*,[4] and inhibition of N-type calcium channels may inhibit norepinephrine release and result in cardiovascular effects.[26]

The remaining FAERS case of cardiovascular adverse events reported factors affecting causality assessment and was unlikely related to levetiracetam. This one case reported increased PVCs in a neonate with pre-existing PVCs.

We identified one FAERS case reporting the unlabeled event of rhabdomyolysis with levetiracetam in the pediatric population with evidence of a possible causal association. Rhabdomyolysis and CK elevation have also been reported with levetiracetam in pediatric and adult populations,[20,27-32] but a probable causal association has not been established because of confounding factors. Although all these cases reported a plausible temporal relationship with levetiracetam administration and positive dechallenge after levetiracetam discontinuation, all of these cases also report seizures prior to the initiation of levetiracetam and onset of rhabdomyolysis or CK elevation. Tonic-clonic seizures may cause CK elevation and are a nontraumatic exertional cause of rhabdomyolysis.[33,34] Therefore, it is unclear in our case whether the rhabdomyolysis or CK elevation occurred secondary to the seizures or levetiracetam administration.

OSE identified the signals of rhabdomyolysis and CK elevation with levetiracetam in FAERS and the literature prior to this pediatric review. OSE and the Office of New Drugs (OND) evaluated the signal and decided to continue pharmacovigilance with no labeling changes for rhabdomyolysis or CK elevation.

We identified one FAERS case reporting the unlabeled event of encephalopathy with levetiracetam in the pediatric population. This case provides evidence of a possible causal association of encephalopathy with levetiracetam because of the plausible temporal relationship and positive dechallenge after levetiracetam discontinuation. However, the case reports a supratherapeutic level of levetiracetam and other factors that may affect the causality assessment (acute renal failure, metabolic acidosis, respiratory distress) and lacks information regarding concomitant medications. Encephalopathy with levetiracetam has also been reported in the adult population, with and without renal failure.[35-37]

The association of levetiracetam with encephalopathy-related adverse events provides biologic plausibility supporting the possible association of levetiracetam with encephalopathy. Although levetiracetam is not labeled for encephalopathy, it is labeled for signs and symptoms of encephalopathy, including behavioral abnormalities, somnolence and fatigue, coordination difficulties, confusional state, sedation, dyskinesia, and coma in the context of overdose.

No clear patterns or trends suggested a new safety signal associated with the other reported serious unlabeled adverse events in the pediatric case series.

5 CONCLUSION

We identified 276 FAERS cases with levetiracetam in the U.S. pediatric population reporting a serious outcome, including 22 deaths. All 22 death cases reported alternative etiologies for the death or did not provide adequate information for causality assessment. Our evaluation of postmarketing adverse event reports does not suggest any new or unexpected pediatric safety concerns with levetiracetam at this time. The majority of reported drug event combinations were consistent with the known risks described in the labeling, or were disease-related or indication-related. We identified five cases related to the unlabeled events of cardiovascular adverse events, rhabdomyolysis, or encephalopathy with a possible causal association. No clear patterns or trends suggested a new safety signal associated with the other reported serious unlabeled adverse events in the pediatric case series.

6 RECOMMENDATIONS

We will continue routine pharmacovigilance for all pediatric adverse events associated with the use of levetiracetam, including cardiovascular adverse events, rhabdomyolysis, and encephalopathy as adverse events of interest in all patient populations.

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8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

National Sales Perspectives (NSP)

The QuintilesIMS 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.

QuintilesIMS, Total Patient Tracker (TPT)

The QuintilesIMS, Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the VectorOne® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. VectorOne® receives over 2.1 billion prescription claims per year. No statistical tests were conducted to determine whether statistically significant changes occurred over time; therefore, all changes over time or between products should be considered approximate and may be due to random error.

Hospital Visit Analyzer (HVA)

The Hospital Visit Analyzer (HVA) provides hospital inpatient and outpatient encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from 2002, is collected weekly and monthly, and is available 25-30 days after the end of each monthly period. This robust data set includes >700 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include over 13 million patients and 60 million visits per year projected to approximately 37 million inpatient visits and 560 million outpatient (including Emergency Department) visits per year, representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data; location of initiation of each service within the hospital setting of care (for example, Pediatric, Intensive Care Units) by day for each patient's entire stay; and patient demographics and admission/discharge characteristics. HVA is representative geographically and across payer types, such as commercial insurers, Medicare and Medicaid.

The QuintilesIMS (QI) hospital sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (such as children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the QI hospital data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of QI's hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown QI's patient level data to be representative and accurate across multiple therapeutic areas.

8.2 APPENDIX B. 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 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.

8.3 APPENDIX C. 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
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, Generalised 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

8.4 APPENDIX D. 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.

8.5 APPENDIX E. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=276)

FAERS Case #	Version #	Manufacturer Control #
12968620	1	
13025491	1	US-UCBSA-2016047791
13025492	1	US-UCBSA-2016047786
13025493	1	US-UCBSA-2016047787
13025494	1	US-UCBSA-2016047788
13025499	1	US-UCBSA-2016047636
13025500	1	US-UCBSA-2016047789
13025541	1	US-UCBSA-2016047792
13025542	1	US-UCBSA-2016047790
10280172	1	US-UCBSA-2014004623
10280183	1	US-UCBSA-2014004624
10884951 10527229 (duplicate)	 1	
11610875	1	
10763382	1	2014015151
11596490	1	US-JNJFOC-20150924527
11992572	1	US-UCBSA-2015010946
9330858	1	
 10462327 10637629 (duplicate) 10809822 (duplicate) 10569659 (duplicate) 10463519 (duplicate) 10484082 (duplicate)	 1 1 1 1 1 1	US-ROXANE LABORATORIES, INC.-2014-RO-01386RO US-GLENMARK PHARMACEUTICALS EUROPE LIMITED- 2014GMK012323 CC15-0144 GB-AUROBINDO-AUR-APL-2014-11580 US-DRREDDYS-USA/USA/14/0043031 2014HINLIT0855
11138725	1	PHHY2015US062564
11986867	1	US-UCBSA-2015005415
12891849 12347331 (duplicate)	1 1	US-UCBSA-2016040737 US-UCBSA-2016015477
10467497 10440710 (duplicate)	1 2	US-UCBSA-2014012193 US-AUROBINDO-AUR-APL-2014-09585
11994332	1	US-UCBSA-2015031332
10947110	2	US-JNJFOC-20140709882
9604661 10366946 (duplicate) 9594978 (duplicate)	1 1 1	US-UCBSA-099690 2013SP006895 AUR-APL-2013-08123
10338051	1	
11992512	1	US-UCBSA-2015007786
11743759	1	US-UCBSA-2015035898
11811996	2	US-ENDO PHARMACEUTICALS INC.-2015-004552
9627919	1	US-LUNDBECK-DKLU1093117
11994059	1	US-UCBSA-2015027357
10284815	1	
12875286	1	US-UCBSA-2016039987
10957787	1	US-BAXTER-2015BAX015494
11773868	2	US-LUNDBECK-DKLU2006880
9499636	1	
9627294	1	US-LUNDBECK-DKLU1085307

FAERS Case #	Version #	Manufacturer Control #
9554651	2	US-PFIZER INC-2013271317
10937062 (duplicate)	2	US-JNJFOC-20130914893
9585516 (duplicate)	1	2013SP006896
9593093 (duplicate)	1	AUR-APL-2013-08120
11987508	1	US-UCBSA-2015025044
10563294	1	US-PFIZER INC-2014302829
12092934	1	US-UCBSA-2016005584
10937130	2	US-JNJFOC-20141021540
12239303	3	GXBR2016US000918
9717325	2	US-LUNDBECK-DKLU1095521
13009299	1	US-UCBSA-2016034534
10308097	1	
12067186	1	US-JNJFOC-20160116381
10154712	1	
10763587	1	2014014735
11814737	3	US-UCBSA-2015039403
11997416	1	US-ABBVIE-16P-163-1550128-00
11212304	1	
12120329	1	PHEH2016US004642
10710235	1	US-UCBSA-2015000652
10762099	1	2014017201
11724714	3	US-UCBSA-2015007784
11986744	1	US-UCBSA-2015005431
11986869	1	US-UCBSA-2014017201
11992502	1	US-UCBSA-2015007789
11376392	1	US-UCBSA-2015025270
11688754	1	US-UCBSA-2015027944
10754191	1	US-UCBSA-2015002165
10763347	1	2014014775
11986699	1	US-UCBSA-2015002892
11987464	1	US-UCBSA-2015012620
12402999	1	US-UCBSA-2016019075
12854838	1	US-UCBSA-2016039095
10911932	2	US-MERCK-1503USA005864
11210945	1	US-ALEMBIC PHARMACEUTICALS LIMITED-2015SCAL000253
10538046	1	
10978804	1	
11102056	1	US-GLENMARK PHARMACEUTICALS EUROPE LIMITED-2015GMK016749
12556359	1	
10229723	1	
9664103	1	
10359404	1	
10573895	1	PHHY2014US140646
10914374	1	US-GLAXOSMITHKLINE-US2015GSK032307
11986760 (duplicate)	1	US-UCBSA-2015006226
10936907	2	US-JNJFOC-20141006637
10570422	1	US-UCBSA-2014016422
11309928	1	US-LUNDBECK-DKLU2001857
11417503	1	US-LUNDBECK-DKLU2003113
11987472	1	US-UCBSA-2014020533
10868339	1	US-LUNDBECK-DKLU1109028
10936943 (duplicate)	2	US-JNJFOC-20150214623
11590994	1	US-AUROBINDO-AUR-APL-2015-08832
11609156	1	US-LUNDBECK-DKLU2004799

FAERS Case #	Version #	Manufacturer Control #
9344494	1	
9458644	4	AUR-APL-2013-06565
10930623	1	US-JNJFOC-20150309296
10787791 (duplicate)	2	US-UCBSA-2015003217
10925266	1	2014007865
11886797	1	US-UCBSA-2015043273
11781854 (duplicate)	1	US-UCBSA-2015037232
11986413	1	US-UCBSA-2014021078
11994111	1	US-UCBSA-2015027470
10387685	1	US-UCBSA-2014008776
10936857 (duplicate)	2	US-JNJFOC-20140719676
10655467	1	US-UCBSA-2014021676
9832815 (duplicate)	1	US-GLAXOSMITHKLINE-B0961592A
10655507 (duplicate)	1	US-UCBSA-2014021673
9828374 (duplicate)	1	US-GLAXOSMITHKLINE-B0960875A
11722841	1	US-LUNDBECK-DKLU2006225
		US-AUROBINDO-AUR-APL-2014-09638
10570111	2	US-DRREDDYS-USA/USA/14/0043032
10463561 (duplicate)	1	US-GLENMARK PHARMACEUTICALS EUROPE LIMITED-
10637635 (duplicate)	1	2014GMK012324
10809784 (duplicate)	1	CC15-0145
9593370	9	US-ALEXION-A201301855
11289601	2	US-UCBSA-2015022156
11992503	1	US-UCBSA-2015007136
9330861	1	
9903010	2	PHEH2014US002487
9885961 (duplicate)	1	US-GLAXOSMITHKLINE-A1060312A
10218584 (duplicate)	1	US-LUNDBECK-DKLU1100427
9890963 (duplicate)	2	US-ABBVIE-14P-163-1199174-00
9879579 (duplicate)	2	US-UCBSA-111075
12400233	1	
11992618	1	US-UCBSA-2015012202
12756087	1	US-UCBSA-2016035334
11819701	1	US-JNJFOC-20151118874
10896063	1	US-UCBSA-2015005669
11665452	1	
11986785	1	US-UCBSA-2014014097
10763517 (duplicate)	1	2014014097
11986868	1	US-UCBSA-2015006241
10922916 (duplicate)	1	US-LUNDBECK-DKLU1109875
10949452 (duplicate)	1	US-ABBVIE-15P-163-1363323-00
11345803 (duplicate)	1	US-ABBVIE-15P-163-1358859-00
10937146	2	US-JNJFOC-20150217719
10655468	1	US-UCBSA-2014021672
9832816	1	US-GLAXOSMITHKLINE-B0961593A
10655469	1	US-UCBSA-2014021675
9832818	1	US-GLAXOSMITHKLINE-B0961595A
10785131	1	US-UCBSA-2015002928
9707205	1	US-JNJFOC-20131110844
9529176	1	US-LUNDBECK-DKLU1089070
13053284	1	
11807698	2	US-UCBSA-2015030819
12628471	1	
10337992	1	
10527924	1	US-UCBSA-2014014737
12228030	1	US-UCBSA-2015040834
11450997	1	US-DRREDDYS-USA/USA/15/0050394

FAERS Case #	Version #	Manufacturer Control #
12456112	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2016US-117772
10412605	1	
11430371	1	PHEH2015US007300
10752846	1	US-LUNDBECK-DKLU1108066
10766037 (duplicate)	2	US-PFIZER INC-2015045046
11694314	1	US-GLAXOSMITHKLINE-US2015GSK156607
10925583	1	2014000946
11828883	1	US-LUNDBECK-DKLU2007786
11993981	1	US-UCBSA-2015026124
11434756 (duplicate)	1	PHEH2015US016655
10655505	1	US-UCBSA-2014021671
9824189 (duplicate)	1	US-GLAXOSMITHKLINE-B0960845A
11128836	2	US-UCBSA-2015015972
12833558	1	US-TARO-2016TAR00832
12093761	1	
9921980	1	
10494474	1	
10938900	2	US-JNJFOC-20140200985
10924205 (duplicate)	1	108754U
10544204	1	
11138768	1	PHHY2015US061717
10472342	1	2014PRN00023
11061665 (duplicate)	1	CC14-1676
10435265 (duplicate)	1	US-AUROBINDO-AUR-APL-2014-09470
10453454 (duplicate)	2	US-UCBSA-2014011514
10488794 (duplicate)	1	2014AJA00031
9922236	1	
10365229	1	
10344230	1	
10040785	2	PHHY2013US035945
10727062	1	
12337347	1	
11587920	1	US-MEDA-2014100053
12114090	1	US-UCBSA-2016005924
12133968	1	PHEH2016US004476
12123587	1	
10938909	2	US-JNJFOC-20140401813
11450996	1	US-DRREDDYS-USA/USA/15/0050410
11620847 (duplicate)	1	US-LPDUSPRD-20150780
10655509	1	US-UCBSA-2014021674
9832817 (duplicate)	1	US-GLAXOSMITHKLINE-B0961594A
10925509	1	122949U
11169388	1	US-GLAXOSMITHKLINE INC.-US2015GSK077164
11430166 (duplicate)	2	PHEH2015US010166
12069431	1	US-HETERO LABS LTD-1047653
9792004	1	US-UCBSA-107064
10404188	1	PHEH2012US000565
10565888	1	US-UCBSA-2014016808
12609446	1	US-LUPIN PHARMACEUTICALS INC.-2015-03191
12609486	1	US-LUPIN PHARMACEUTICALS INC.-2015-04022
10871090	1	US-LUNDBECK-DKLU1108975
11318342	1	US-LUNDBECK-DKLU2002117
11375560	2	US-UCBSA-2015025032
10657923	2	PHHY2014US150911
11387847	4	PHEH2014US021399
10276391	1	
10358569	5	PHHY2014US079448

FAERS Case #	Version #	Manufacturer Control #
9347911	1	
9973244	1	085435
11574362	1	
12411977	1	
11871672	1	PHEH2015US027008
13051573	1	
10689309	1	US-ACCORD-027916
10688794 (duplicate)	1	US-AUROBINDO-AUR-APL-2014-13746
12950312	1	US-SAGENTPRD-2016-US-000055
10547996	1	
13023384	1	
10906498	4	US-UCBSA-2015001084
11994764	1	US-UCBSA-2015035642
11890449 (duplicate)	2	US-ABBVIE-15P-163-1530538-00
10551133	1	US-UCBSA-2014015208
12073229	1	
11518762	2	US-TEVA-594853USA
11516557 (duplicate)	4	US-ACTAVIS-2015-19742
12216308 (duplicate)	1	US-AUROBINDO-AUR-APL-2015-06710
11522887 (duplicate)	2	US-UCBSA-2015029385
11535054 (duplicate)	2	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2015US-103337
11575289 (duplicate)	2	US-DEXPHARM-20151679
11694461 (duplicate)	1	US-ROXANE LABORATORIES, INC.-2015-RO-01787RO
11390594 (duplicate)	2	US-ACCORD-032808
12543906	2	US-ALVOGEN-2016-ALVOGEN-025864
12541267 (duplicate)	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-16-01243
12546391 (duplicate)	2	US-TEVA-675198USA
12551503 (duplicate)	1	US-BAUSCH-BL-2016-016247
12552367 (duplicate)	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2016US-120187
12544270 (duplicate)	2	US-UCBSA-2016025617
12573183 (duplicate)	1	US-AUROBINDO-AUR-APL-2016-09401
12572939 (duplicate)	1	US-ACCORD-042454
9587733	3	US-UCBSA-099256
9540724 (duplicate)	2	US-LUNDBECK-DKLU1093726
12977253	1	US-ACCORD-045766
11725028	1	US-UCBSA-2014010795
10924802 (duplicate)	1	2014010795
10132962	1	US-JNJFOC-20140411956
9604628	1	US-UCBSA-099669
9595014 (duplicate)	1	AUR-APL-2013-08093
10366941 (duplicate)	1	2013SP006864
12928047	1	US-UCBSA-2016027926
11682087	2	US-ROCHE-1652414
11667886 (duplicate)	2	US-UCBSA-2015033873
11687712 (duplicate)	1	US-LUNDBECK-DKLU2005893
11690752 (duplicate)	1	US-ENDO PHARMACEUTICALS INC.-2015-003675
11696082 (duplicate)	2	US-ABBVIE-15P-163-1490343-00
11706232 (duplicate)	2	US-ABBVIE-15P-163-1496154-00
11980855 (duplicate)	1	US-BAUSCH-BL-2016-001874
10644455	1	US-LUNDBECK-DKLU1106304
9882976	1	20140023
11358852	1	
9604563	1	US-UCBSA-099703
10366947 (duplicate)	1	2013SP006897
9595051 (duplicate)	1	AUR-APL-2013-08118
9661580	1	AUR-APL-2013-09031
9337057	1	US-UCBSA-088151

FAERS Case #	Version #	Manufacturer Control #
11993677	1	
9325745	1	
10338002	1	
11217538	1	PHHY2015US056358
12818604	2	PHHY2016US135985
11457307	1	US-ACCORD-033425
9625545	2	US-ROXANE LABORATORIES, INC.-2013-RO-01671RO
11990404	5	US-MEDTRONIC-1047217
11371531	2	US-UCBSA-2015024886
11626585	1	US-UCBSA-2014014617
12677640	1	US-UCBSA-2016031804
11660526	1	US-KNIGHT THERAPEUTICS (USA) INC.-1043373
12536849	1	US-CONCORDIA PHARMACEUTICALS INC.-GSH201607-003469
10283315	1	
11833979	2	US-ENDO PHARMACEUTICALS INC.-2015-004879
11986783	1	US-UCBSA-2014020682
10772415	1	US-ACCORD-028505
11381740 (duplicate)	1	PHHY2015US095420
12070980 (duplicate)	1	US-PRINSTON PHARMACEUTICAL INC.-2016PRN00029
11360754 (duplicate)	1	US-ACTAVIS-2015-16475
11398763 (duplicate)	1	US-LUPIN PHARMACEUTICALS INC.-2015-02468
10783924 (duplicate)	2	US-ALVOGEN-2015AL000231
11546457 (duplicate)	2	US-LPDUSPRD-20150716
12076396 (duplicate)	1	US-AJANTA PHARMA USA INC.-1047787
12637664	1	US-ABBVIE-15P-163-1468037-00
9547821	1	2013-01241
9494308	1	LEVE20130007
9474831 (duplicate)	1	PHHY2013US089291
9472242 (duplicate)	1	US-TEVA-427629USA
9482594 (duplicate)	1	US-MYLANLABS-2013S1018436
9495212 (duplicate)	1	US-ROXANE LABORATORIES, INC.-2013-RO-01446RO
9500007 (duplicate)	1	US-UCBSA-096895
9513995 (duplicate)	1	US-TARO PHARMACEUTICALS U.S.A., INC-2013SUN04604
9537344 (duplicate)	1	US-MUTUAL PHARMACEUTICAL COMPANY, INC.-LVTM20130005
9498847 (duplicate)	1	USA/USA/13/0034289
9486424 (duplicate)	1	2013AP007497
9511042 (duplicate)	1	FK201303689
9507294 (duplicate)	1	2013/166
9612544 (duplicate)	1	20130510
9490443 (duplicate)	2	AUR-APL-2013-07063
12596567 (duplicate)	1	US-ENDO PHARMACEUTICALS INC-LEVE20130007
12241983	1	US-UCBSA-2016012034
10910672	1	US-ABBVIE-14P-163-1315124-00
9407522	1	US-JNJFOC-20130706928
10591531	1	US-LUNDBECK-DKLU1105730
11856210	1	US-MYLANLABS-2015M1027431
10469369	2	PHHY2014US115035
10863598	2	PHHY2014US130071
9353102	1	
10495402	1	ADR-2014-00656
12529793	1	
10196893	3	US-UCBSA-122082
13037204	1	US-PFIZER INC-2016576096
11466963	1	US-UCBSA-2015028140
12935901	1	
9422050	1	
10368217	1	

FAERS Case #	Version #	Manufacturer Control #
10341281	3	US-UCBSA-2014005960
12609465	1	US-LUPIN PHARMACEUTICALS INC.-2015-03193
13075101	1	US-ZYDUS-013023
12938844 (duplicate)	1	US-ALVOGEN-2016-ALVOGEN-086381
12961884 (duplicate)	1	US-UCBSA-2016043086
13063146 (duplicate)	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2016US-129995
13067297 (duplicate)	1	US-APOTEX-2016AP016018
13069475 (duplicate)	1	US-TEVA-723025USA
11195932	1	
10655379	1	
12936305	1	
10925036	1	2014012916
10763544 (duplicate)	1	2014014153
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9669872	1	AUR-APL-2013-08303
12406007	2	US-LUPIN PHARMACEUTICALS INC.-E2B_00005458
12257330	1	PHHY2016US047901
12238851 (duplicate)	1	US-MDT-ADR-2016-00628
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10796302	2	US-UCBSA-2015000299
10405554	1	US-LUPIN PHARMACEUTICALS INC.-E2B_00002383
9396608	1	US-UCBSA-091056
10248639	1	
10397614	1	PHHY2014US102479
11694035	3	US-APOTEX-2015AP013867

FAERS Case #	Version #	Manufacturer Control #
		US-TEVA-508022USA
10453143	4	PHHY2014US109596
10440298 (duplicate)	1	PHHY2015US086433
11309603 (duplicate)	1	US-MORTON GROVE PHARMACEUTICALS, INC.-1042238
11542866 (duplicate)	1	ADR-2015UNK160
11368068 (duplicate)	1	2014AP004469
10442477 (duplicate)	1	US-TARO PHARMACEUTICALS U.S.A., INC-2014SUN02067
10452745 (duplicate)	1	US-TARO PHARMACEUTICALS U.S.A., INC-2015SUN01692
11311579 (duplicate)	1	US-ROXANE LABORATORIES, INC.-2014-RO-01372RO
10453866 (duplicate)	1	US-DRREDDYS-USA/USA/14/0043023
10463586 (duplicate)	1	US-ZYDUS-005001
10469560 (duplicate)	2	US-GLENMARK PHARMACEUTICALS EUROPE LIMITED-
10900492 (duplicate)	1	2015GMK014609
11143611 (duplicate)	2	US-ACCORD-030920
11291791 (duplicate)	3	US-ACTAVIS-2015-15069
11294518 (duplicate)	1	US-H14001-15-01392
11340749 (duplicate)	1	US-FRESENIUS KABI-FK201503660
11359780 (duplicate)	4	US-DRREDDYS-USA/USA/15/0049880
11381186 (duplicate)	1	US-ROXANE LABORATORIES, INC.-2015-RO-01322RO
10435269 (duplicate)	2	US-AUROBINDO-AUR-APL-2014-09467
10446660 (duplicate)	6	US-RANBAXY-2014US-85163
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11117473 (duplicate)	3	US-AUROBINDO-AUR-APL-2015-04283
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11318478 (duplicate)	1	US-LUPIN PHARMACEUTICALS INC.-2015-01732
10381004 (duplicate)	1	2014/056
11922852 (duplicate)	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2016US-109690
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11292564	2	PHEH2015US014062
11215679	2	US-APOTEX-2015AP009976
12613509	1	US-LUPIN PHARMACEUTICALS INC.-2016-03330
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FAERS Case #	Version #	Manufacturer Control #
11549994	2	US-TEVA-596583USA
11546455 (duplicate)	1	PHHY2015US112459
11580820 (duplicate)	2	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-065467
11610805 (duplicate)	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-066346
11561396 (duplicate)	1	US-APOTEX-2015AP013019
11575037 (duplicate)	1	US-TARO PHARMACEUTICALS USA.,INC-2015SUN02058
11617788 (duplicate)	1	US-PRINSTON PHARMACEUTICAL INC.-2015PRN00082
11540814 (duplicate)	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-15-01713
11544838 (duplicate)	2	US-ACTAVIS-2015-20327
11558297 (duplicate)	1	US-GLENMARK PHARMACEUTICALS INC, USA.-2015GMK019688
11558550 (duplicate)	1	US-LUPIN PHARMACEUTICALS INC.-2015-02943
11573265 (duplicate)	1	US-BAUSCH-BL-2015-022136
11574486 (duplicate)	1	US-FRESENIUS KABI-FK201504524
11582821 (duplicate)	1	US-HOSPIRA-3020041
11591011 (duplicate)	1	US-INVENTIA-000079
11591012 (duplicate)	1	US-ALKEM-001252
11591020 (duplicate)	1	US-INDICUS PHARMA-000365
11591848 (duplicate)	1	US-ACCORD-034068
11614967 (duplicate)	1	US-DRREDDYS-USA/USA/15/0053189
11617960 (duplicate)	1	US-ZYDUS-009179
11761882 (duplicate)	1	US-ROXANE LABORATORIES, INC.-2015-RO-01935RO
11556335 (duplicate)	1	US-IMPAX LABORATORIES, INC-2015-IPXL-00955
11557902 (duplicate)	1	US-ALVOGEN-2015AL003777
11558316 (duplicate)	2	US-UCBSA-2015030323
11568533 (duplicate)	3	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2015R1-103811
11572306 (duplicate)	1	US-IPCA LABORATORIES LIMITED-IPC201509-000643
11618582 (duplicate)	1	US-ORCHID HEALTHCARE-1042809
11621543 (duplicate)	1	US-AJANTA PHARMA USA INC.-1042838
11636269 (duplicate)	1	US-HETERO LABS LTD-1043027
11644018 (duplicate)	3	US-AUROBINDO-AUR-APL-2015-09300
13038769	1	UUS-UCBSA-2016042819
12946146 (duplicate)	1	US-PFIZER INC-2016560474
13002398 (duplicate)	1	US-DEXPHARM-20162349
13008184 (duplicate)	1	US-ALVOGEN-2016-ALVOGEN-087279
13022137 (duplicate)	1	US-HETERO LABS LTD-1061013
13043327 (duplicate)	1	US-TOLMAR INC.-1060974S-ACCORD-046568
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10582330	2	US-UCBSA-2014011653
9516527	2	US-ROXANE LABORATORIES, INC.-2013-RO-01499RO
11994666	1	US-UCBSA-2015029315

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