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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):	Topamax (topiramate)
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Applicant/Sponsor:	Janssen Pharmaceuticals, Inc.
OSE RCM #:	2016-479

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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 Topamax (topiramate) in pediatric patients.

Topamax (topiramate) was first approved in 1996 and is indicated as initial monotherapy for partial onset or primary generalized tonic-clonic seizures in patients ≥ 2 years of age, as adjunctive therapy for partial onset seizures or primary generalized tonic-clonic seizures in adults and pediatric patients ages 2-16 years, as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome in patients ≥ 2 years of age, and as prophylaxis of migraine headache for patients ≥ 12 years of age. The latest pediatric labeling change occurred on March 28, 2014, when topiramate was approved for the prophylaxis of migraine headache in patients ≥ 12 years of age.

From March 2014 through February 2016, a total of 4.1 million patients received a dispensed prescription for topiramate, of which, the pediatric population aged 0-17 years accounted for 7% of the total patients. Among all the pediatric age groups, the largest use of topiramate was in patients aged 12-17 years; however, use was seen in all the age groups examined.

We identified 76 FAERS cases with topiramate in the U.S. pediatric population reporting a serious outcome. Three of these FAERS cases reported death as an outcome; however, a causal association could not be established because of insufficient case details and consideration of underlying diseases and concomitant medications. Our evaluation of postmarketing adverse event reports does not suggest any new or unexpected pediatric safety concerns with topiramate 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 three cases related to the unlabeled events of anorexia nervosa and bulimia nervosa. These three cases did not contain sufficient case details for assessment, but the role of topiramate cannot be ruled out. No clear patterns or trends suggested a new safety signal associated with the other reported serious unlabeled adverse events, i.e., acute kidney injury, hypovolemic shock, cardiac arrest, respiratory arrest, and respiratory failure. The unlabeled events of acute kidney injury and hypovolemic shock occurred in one case secondary to acute hepatic failure (labeled event).

We will continue routine pharmacovigilance for all pediatric adverse events associated with the use of topiramate, including anorexia nervosa, bulimia nervosa, and hepatic failure as adverse events of interest in all patient populations.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Topamax (topiramate) is available in oral tablets (containing 25 mg, 50 mg, 100 mg, or 200 mg of topiramate) and oral sprinkle capsules (containing 15 mg or 25 mg of topiramate).

Table 1 summarizes the U.S. approval history of Topamax (topiramate).

Table 1. U.S. Approval History of Topamax (Topiramate)

Date of Approval	Indication
12/24/1996	Adjunctive therapy for partial onset seizures in adults
7/23/1999	Adjunctive therapy for partial onset seizures in adults and pediatric patients ages 2-16 years
10/1/1999	Adjunctive therapy for primary generalized tonic-clonic seizures
8/28/2001	Adjunctive therapy for seizures associated with Lennox-Gastaut syndrome in patients ≥ 2 years of age
8/11/2004	Prophylaxis for migraine headache in adults
6/29/2005	Initial monotherapy for partial onset or primary generalized tonic-clonic seizures in patients ≥ 10 years of age
7/15/2011	Initial monotherapy for partial onset or primary generalized tonic-clonic seizures in patients ≥ 2 years of age
3/28/2014	Prophylaxis for migraine headache in patients ≥ 12 years of age

The latest pediatric labeling change occurred on March 28, 2014, when topiramate was approved for the prophylaxis of migraine headache in patients ≥ 12 years of age. The effectiveness of topiramate as prophylaxis for migraine headache in adolescents was established in a multicenter, randomized, double-blind, parallel-group trial. The study enrolled 103 patients (40 male, 63 female) age 12 to 17 years with episodic migraine headaches with or without aura. The 100 mg topiramate dose produced a statistically significant treatment difference relative to placebo of 28% reduction from baseline in the monthly migraine attack rate (Topamax PI 2014).

In five randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse reactions with topiramate were mild or moderate in severity. Most adverse reactions occurred more frequently during the titration period than during the maintenance period. Among adverse reactions with onset during titration, approximately half persisted into the maintenance period (Topamax PI 2014).

The pediatric migraine trials observed the following (Topamax PI 2014; Kapcala 2014):

- the most commonly observed adverse reactions were paresthesia, upper respiratory tract infection, anorexia, and abdominal pain.
- the major safety findings were cognitive dysfunction, metabolic acidosis, hyperammonemia, rare kidney stones, and paresthesia.
- the most common cognitive adverse reactions were difficulty with concentration or attention.

The pediatric migraine trials also observed the following (Topamax PI 2014; Kapcala 2014):

- markedly abnormally low serum bicarbonate values indicative of metabolic acidosis.
- abnormally increased creatinine, BUN, uric acid, chloride, ammonia, total protein, and platelets.
- abnormally decreased phosphorus and bicarbonate.
- notable changes (increases and decreases) from baseline in systolic blood pressure, diastolic blood pressure, and pulse.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current approved label for topiramate (December 18, 2014) provides the following information excerpted from pertinent sections (Topamax PI 2014):

5 WARNINGS AND PRECAUTIONS

- **5.1 Acute Myopia and Secondary Angle Closure Glaucoma:** Untreated elevated intraocular pressure can lead to permanent visual loss. The primary treatment to reverse symptoms is discontinuation of TOPAMAX as rapidly as possible.
- **5.2 Visual Field Defects:** These have been reported independent of elevated intraocular pressure. Consider discontinuation of TOPAMAX.
- **5.3 Oligohidrosis and Hyperthermia:** Monitor decreased sweating and increased body temperature, especially in pediatric patients.
- **5.4 Metabolic Acidosis:** Baseline and periodic measurement of serum bicarbonate is recommended. Consider dose reduction or discontinuation of TOPAMAX if clinically appropriate.
- **5.5 Suicidal Behavior and Ideation:** Antiepileptic drugs increase the risk of suicidal behavior or ideation.
- **5.6 Cognitive/Neuropsychiatric Adverse Reactions:**
    - TOPAMAX may cause cognitive dysfunction. Patients should use caution when operating machinery including automobiles. Depression and mood problems may occur in epilepsy and migraine populations.

    - Pediatric patients, Migraine:
      The incidence of cognitive adverse reactions was increased in TOPAMAX-treated patients (7%) versus placebo (4%) in pooled, double-blind placebo-controlled studies in which adolescent patients (12 to 17 years) were randomized to placebo or one of several fixed daily doses of TOPAMAX (50 mg, 100 mg, 200 mg).

      The risk for cognitive adverse reactions was dose-dependent, and was particularly evident at the 200 mg dose. This risk for cognitive adverse reactions was also greater in younger patients (6 to 11 years) than in older patients (12 to 17 years). The most common cognitive adverse reaction in these trials was difficulty with concentration/attention. Cognitive adverse reactions most commonly developed in the titration period and sometimes persisted into the maintenance period.
- **5.7 Fetal Toxicity:** TOPAMAX use during pregnancy can cause cleft lip and/or palate and reduced fetal weights.

- **5.8 Withdrawal of Antiepileptic Drugs (AEDs):** Withdrawal of TOPAMAX should be done gradually.
- **5.9 Sudden Unexplained Death in Epilepsy (SUDEP)**
- **5.10 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid Use):** Patients with inborn errors of metabolism or reduced mitochondrial activity may have an increased risk of hyperammonemia. Measure ammonia if encephalopathic symptoms occur.
- **5.11 Kidney Stones:** Use with other carbonic anhydrase inhibitors, other drugs causing metabolic acidosis, or in patients on a ketogenic diet should be avoided.
- **5.12 Hypothermia with Concomitant Valproic Acid (VPA) Use:** Hypothermia has been reported with and without hyperammonemia during topiramate treatment with concomitant valproic acid use.
- **5.13 Paresthesia:** Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX in adult and pediatric patients.
- **5.14 Adjustment of Dose in Renal Failure:** Dosage adjustment may be required in patients with reduced renal function.
- **5.15 Decreased Hepatic Function:** In hepatically impaired patients, TOPAMAX should be administered with caution as the clearance of topiramate may be decreased.
- **5.16 Monitoring: Laboratory Tests:**
    - Topiramate treatment was associated with changes in several clinical laboratory analytes in randomized, double-blind, placebo-controlled studies.

      Topiramate treatment causes non-anion gap, hyperchloremic metabolic acidosis manifested by a decrease in serum bicarbonate and an increase in serum chloride. Measurement of baseline and periodic serum bicarbonate during TOPAMAX treatment is recommended [see Warnings and Precautions (5.4)].

      TOPAMAX treatment with or without concomitant valproic acid (VPA) can cause hyperammonemia with or without encephalopathy [see Warnings and Precautions (5.10)].

    - Migraine

      In pooled double-blind studies in pediatric patients (6 to 17 years), an increased risk for certain abnormalities (value outside normal reference range) in selected clinical laboratory analytes measured in blood has been observed during topiramate treatment of pediatric patients compared to placebo-treated patients. In some instances, abnormalities were also observed at the end of the trial at the final visit and the changes were considered markedly abnormal.

      For patients 12 to 17 years, the following were noted to be abnormally increased more frequently with topiramate than with placebo: BUN, creatinine, uric acid, chloride [see Warnings and Precautions (5.4)], ammonia [see Warnings and Precautions (5.10)], total protein, and platelets. The following were abnormally decreased in some subjects: phosphorus and bicarbonate [see Warnings and Precautions (5.4)].

For patients 6 to 11 years, the following were noted to be abnormally increased more frequently with topiramate than with placebo: alkaline phosphatase, creatinine and eosinophils. Analytes abnormally decreased were: total white count and neutrophils.

6 ADVERSE REACTIONS

The most common (≥ 10% more frequent than placebo or low-dose TOPAMAX in monotherapy) adverse reactions at recommended dosing in adult and pediatric controlled, epilepsy clinical trials were paresthesia, anorexia, weight decrease, speech disorder related speech problem, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, abnormal vision, and fever. The most common (≥ 5% more frequent than placebo) adverse reactions at recommended dosing in adult and adolescent controlled, migraine clinical trials were paresthesia, anorexia, weight decrease, difficulty with memory, taste perversion, upper respiratory tract infection, abdominal pain, diarrhea, hypoesthesia, and nausea.

6.2 Postmarketing and Other Experience

These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, maculopathy, pancreatitis, and pemphigus.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Adjunctive Treatment for Partial Onset Epilepsy in Infants and Toddlers (1 to 24 months)
Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome.

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 various settings of care where topiramate is distributed by the manufacturer. Sales distribution data for 2015 showed that approximately 86% of topiramate bottles were sold to U.S. outpatient retail pharmacies, followed by 9% to non-retail settings (mostly long-term care and clinics) and 5% to mail order/specialty pharmacy settings. Based on these results, we examined the drug utilization data for only the U.S. outpatient retail pharmacy settings.

2.1.2 Data Sources Used

The IMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a prescription for topiramate from U.S. outpatient retail pharmacies, stratified by patient age groups (0-1, 2-11, 12-17, 18 years and older) from March 1, 2014 through February 29, 2016, cumulative.

2.2 DRUG UTILIZATION DATA RESULTS

Table 2.

Nationally Estimated Number of Patients with a Dispensed Prescription for Topiramate, Stratified by Patient age, from U.S. Outpatient Retail Pharmacies, March 2014 through February 2016

	March 1, 2014 - February 29, 2016	
	Patient Count N	**Share %**
Topiramate Total Patients	**4,071,291**	**100.0%**
0-17 (age in years)	**267,329**	**6.6%**
0 - 1 years	3,238	1.2%
2-11 years	62,058	23.2%
12-17 years	213,362	79.8%
18 years and older	**3,808,283**	**93.5%**
Unspecified age	**39,523**	**1.0%**

Source: IMS, Vector One®: Total Patient Tracker. March 2014 - February 2016. Extracted April-2016. File: TPT 2016-479 topiramate BPCA April-2016.xls

*Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include <17 years of age (16 years and 11 months).

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 3. See Appendix B for a description of the FAERS database.

Table 3. FAERS Search Strategy

Date of Search	March 1, 2016
Time Periods of Search*	January 31, 2013 - February 29, 2016 March 1, 2014 - February 29, 2016
Search Type	FBIS profile (or product-manufacturer-reporting summary) query FBIS quick query
Product Name(s)	Product active ingredient: topiramate
Search Parameters	All ages, all outcomes, worldwide, MedDRA PTs (v18.1)

* January 31, 2013 is date of data cutoff from previous Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review presented at September 2013 Pediatric Advisory Committee. U.S. approval date of pediatric labeling was March 28, 2014

We identified all U.S. pediatric FAERS reports with a serious outcome received from January 31, 2013 to February 29, 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 topiramate. 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 January 31, 2013 to February 29, 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 topiramate 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 events of interest in the U.S. pediatric population from March 1, 2014 (pediatric labeling change) to February 29, 2016 that are serious unlabeled DECs identified with our data analysis above. We did not identify any additional events of interest with topiramate 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 4,336 total reports for topiramate in all ages and countries from March 1, 2014 to February 29, 2016. Table 4 summarizes the total number of FAERS reports stratified by age and outcome.

Table 4. Total Adult and Pediatric FAERS Reports* From March 1, 2014 to February 29, 2016 With Topiramate

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	2,108 (1231)	1,697 (846)	299 (263)
Pediatrics (0 - <17 years)	346 (163)	**297 (121)‡§**	4 (3)§

* 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.
‡ See Figure 3.2.2
§ One report of U.S. pediatric death was identified among reports not reporting an age.

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 121 U.S. pediatric reports with topiramate reporting a serious outcome from March 1, 2014 to February 29, 2016 (see Table 4). Our pediatric case series included 76 cases, including 3 deaths, after excluding duplicate reports (n=40), transplacental exposure reports (n=4), and miscoded age reports (n=1).

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 5 summarizes the 76 FAERS cases in U.S. pediatric patients with topiramate reporting a serious outcome received by FDA from March 1, 2014 to February 29, 2016.

Table 5. Characteristics of U.S. Pediatric Case Series With Topiramate, Received by FDA From March 1, 2014 to February 29, 2016 (N=76)		
Age	0 - < 1 month	1
	1 month - <2 years	17
	2- < 6 years	23
	6- <12 years	17
	12- < 17 years	18
Sex	Male	39
	Female	35
	Unknown	2
Report Year	2014	32
	2015	41
	2016	3
Reported Reason for Use*	Seizures/epilepsy	51
	Migraine prophylaxis	10
	Infantile spasms	8
	Aggression	3
	Unknown	2
	Chronic pain	1
	Lennox-Gastaut	1
Serious Outcome†	Death	3
	Life-threatening	3
	Hospitalized	20
	Disability	2
	Congenital anomaly	0
	Required Intervention	0
	Other serious	60

* Seizures/epilepsy includes the following reported reasons for use: seizures, epilepsy, status epilepticus, generalized tonic-clonic seizures, myoclonic epilepsy, partial seizures, frontal lobe 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=3)

We identified three cases with topiramate reporting death as an outcome in the pediatric population. Two cases were likely disease related and reported several other concomitant antiepileptic medications. One case reported an intentional suicide with ingestion of topiramate and did not contain sufficient case details for assessment. The cases are described below.

FAERS #11138725v1, MCN: PHHY2015US062564, USA, 2015: a literature case reported a 9 week old male who was placed on a ketogenic diet for treatment of refractory seizures (Cobo, Sankar, et al. 2015). At 13 months of age, the patient developed a respiratory infection and died. Medical history included multifocal complex partial seizures, occasionally associated with apnea and respiratory infections, and vagal nerve stimulator implantation. Medications included topiramate, levetiracetam, lacosamide, rufinamide, clonazepam, phenobarbital, and vitamin B (all received for unknown times).

FAERS #10930623v1, MCN: US-JNJFOC-20150309296, USA, 2015: a consumer reported a 3 year old male who experienced seizures, and the mother inquired about medicinal cannabis sativa for treatment of refractory epilepsy. At an unknown time, the patient experienced a seizure and died. Medical history included epilepsy. Medications included topiramate, levetiracetam, and lorazepam (all received for unknown times).

FAERS #11246197v1, MCN: US-CIPLA LTD.-2015US05286, USA, 2015: a literature case reported a 16 year old of unknown sex who committed intentional suicide by ingesting an unknown amount of topiramate (Watson, Litovitz, et al. 2005). The patient had prehospital cardiac and respiratory arrest and died. Medical history and concomitant medications were not reported.

Reviewer comment: this case was reported in a literature article in 2005, and was also included and presented in the previous Pediatric Postmarket Pharmacovigilance and Drug Utilization Review in 2013 (Simms, Montenegro, et al. 2013).

3.4 SUMMARY OF ALL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=76)

We identified 76 FAERS cases with topiramate in the U.S. pediatric population reporting a serious outcome including the 3 death cases described above, with 190 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 ≥ 3 cases included:

- somnolence and fatigue
- cognitive-related dysfunction (mental status changes, difficulty with concentration, memory, or speech)
- neuropsychiatric disturbances (aggression, abnormal/antisocial behavior, or depression)
- kidney stones
- oligohidrosis and hyperthermia
- myopia and secondary angle closure glaucoma
- decreased appetite, weight loss
- insomnia

Several unlabeled DECs were disease-related or indication-related. Unlabeled DECs related to the patient's underlying disease or indication for use reported in ≥ 3 cases included:

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

The cases reporting ineffective drug and product issues primarily reported seizures with the use of topiramate. We did not identify a trend with any specific topiramate products, lot numbers, or manufacturers associated with these DECs.

We identified 10 FAERS cases with topiramate in the pediatric population reporting a serious outcome with migraine prophylaxis as the reported reason for use. The mean reported age was 12 years (median 13.5 years, range 5-16 years); 4 of these patients were aged < 12 years (unlabeled migraine patient population). The majority of reported DECs were consistent with the known risks described in the labeling, including cognitive-related dysfunction, neuropsychiatric disturbances, pain, fatigue, insomnia, oligohidrosis and hyperthermia, and myopia.

We identified 18 FAERS cases with topiramate reporting a serious outcome in the pediatric population < 2 years of age (unlabeled patient population). A subset analysis of these cases is discussed in section 3.4.2.

We identified seven events of interest that are serious unlabeled DECs, some of which are considered rare and associated with a high drug-attributable risk. These events include anorexia nervosa, bulimia nervosa, acute kidney injury, hypovolemic shock, cardiac arrest, respiratory arrest, and respiratory failure. Our review focuses on these events of interest with topiramate in the US pediatric population.

3.4.1 Serious Unlabeled DECs

We identified six cases reporting seven serious unlabeled DECs of interest with topiramate in the pediatric population. Three cases (FAERS #s 11089420v1, 11089417v1, 11089414v1) reported the development or exacerbation of eating disorder symptoms after topiramate initiation for migraine prophylaxis. These three cases did not contain sufficient case details for assessment, but the role of topiramate cannot be ruled out. One case (FAERS #10476910v1) reported acute kidney injury and hypovolemic shock secondary to acute hepatic failure with topiramate. The events reported in the case (acute hepatic failure, hepatic encephalopathy, hyperammonemia, and acidosis) are consistent with the known risks described in the labeling for topiramate. One case (FAERS #11246197v1) reported cardiac arrest and respiratory arrest secondary to an intentional suicide with ingestion of topiramate and did not contain sufficient case details for assessment. One case (FAERS #11596490v1) reported respiratory failure and seizures. The case lacked sufficient details for assessment, the events may have been disease related, and the case also reported several other concomitant antiepileptic medications. The cases are described below.

ANOREXIA NERVOSA (N=2)

FAERS #11089420v1, MCN: US-ACCORD-030403, USA, 2015: a literature case reported a 13 year old female who developed anorexia nervosa at an unknown time after receiving topiramate 25 mg BID for migraines (Lebow, Chuy, et al. 2015). Symptoms included a weight loss of 11.5 kg, dietary restriction, and nighttime binge eating. The physical sequelae included anergia, amenorrhea, sinus bradycardia, and ST and T wave changes on EKG. It is unknown whether topiramate therapy was continued and the event outcomes were not reported. Medical history included family history of eating disorders, migraines, and vein of Galen malformation treated with coiling. Baseline weight and height were not reported. Concomitant medications were not reported.

FAERS #11089417v1, MCN: US-ACCORD-030402, USA, 2015: a literature case reported a 16 year old female who developed exacerbation of anorexia nervosa at an unknown time after receiving topiramate 50 mg BID for migraines (Lebow, Chuy, et al. 2015). Symptoms included a weight loss of 22.7 kg, dietary restriction, and self-induced vomiting. The physical sequelae included amenorrhea, cold intolerance, orthostatic intolerance, dizziness, fatigue, abdominal pain, and constipation. It is unknown whether topiramate therapy was continued and the event outcomes were not reported. Medical history included postural orthostatic tachycardia syndrome, migraines, and anorexia nervosa. Baseline weight and height were not reported. Concomitant medications were not reported.

BULIMIA NERVOSA (N=1)

FAERS #11089414v1, MCN: US-ACCORD-030405, USA, 2015: a literature case reported a 16 year old female who developed bulimia nervosa at an unknown time after receiving topiramate 150 mg daily for migraines (Lebow, Chuy, et al. 2015). Symptoms included a weight gain of 32 kg, dietary restriction, and binge eating. It is unknown whether topiramate therapy was continued and the event outcomes were not reported. Medical history included postural orthostatic tachycardia syndrome, gastrointestinal mastocytosis, major depressive disorder, and migraines. Baseline weight and height were not reported. Concomitant medications were not reported.

ACUTE KIDNEY INJURY, HYPOVOLEMIC SHOCK (N=1)

FAERS #10476910v1, MCN: US-ACCORD-026080, USA, 2014: a literature case reported an 11 year old male who developed acute hepatic failure, hepatic encephalopathy, hyperammonemia, acidosis, acute kidney injury, and hypovolemic shock while receiving topiramate therapy for epilepsy (Tsien, Cordova, et al. 2014). The patient presented with somnolence and diarrhea and was hospitalized. Initial investigations showed grade IV hepatic encephalopathy with AST 5666 U/L [normal 0-35 U/L], ALT 7890 U/L [normal value 0-35 U/L], GGT 243 U/L [8-78 U/L], bilirubin 5.9 mg/dL [0.3-1.2 mg/dL], INR 10.8 [<1], and ammonia 1350 mcg/dL [40-80 mcg/dL]. The patient also had acidosis with pH 7.1 [7.38-7.44] and lactate 18 mmol/L [0.67-1.8 mmol/L], acute kidney injury with SCr 2.2 mg/dL [0.7-1.3 mg/dL], and hypovolemic

shock. The patient received topiramate for approximately 10 years prior. His topiramate level of 21.2 mcg/mL on admission was within the therapeutic range of 2-25 mcg/ml, but was "significantly elevated" from his previous levels of 5-7 mcg/mL. Other serum antiepileptic blood levels were "within their therapeutic ranges." Topiramate was discontinued and his aminotransferases, ammonia, and coagulopathy "rapidly improved" with resuscitation, fresh frozen plasma, and discontinuation of topiramate. On day 4 of admission, a transjugular liver biopsy revealed severe acute hepatitis and microvesicular steatosis involving 50% of the liver parenchyma consistent with drug-induced liver injury. At the time of the report, the patient continued to improve over the following weeks with normalization of laboratory values but remained ventilator-dependent with impaired mental status. Medical history included cerebral palsy, intellectual disability, and epilepsy. Concomitant medications included phenobarbital, diazepam, and baclofen (all received since infancy and continued throughout the hospitalization).

Reviewer comment: Topiramate is not labeled for acute kidney injury or hypovolemic shock; however, these events occurred secondary to acute hepatic failure. Topiramate is labeled for hyperammonemia and encephalopathy and metabolic acidosis in the Warnings and Precautions section, and for hepatic failure (including fatalities) in the Postmarketing Adverse Reactions section. In addition, the case reports a long latency of 10 years to the onset of possible drug induced liver injury with topiramate.

CARDIAC ARREST, RESPIRATORY ARREST (N=1)

FAERS #11246197v1, MCN: US-CIPLA LTD.-2015US05286, USA, 2015: a literature case reported a 16 year old of unknown sex who committed intentional suicide by ingesting an unknown amount of topiramate (Watson, Litovitz, et al. 2005). The patient had prehospital cardiac and respiratory arrest and died. The case is also described in section 3.3 Summary of Fatal Pediatric Adverse Event Cases.

RESPIRATORY FAILURE (N=1)

FAERS #11596490v1, MCN: US-JNJFOC-20150924527, USA, 2015: a consumer reported a 2 week old male who experienced seizures and respiratory failure while receiving topiramate therapy for seizures. The patient experienced a seizure at 2 weeks of age, and was hospitalized at 1 month of age. At an unknown time after hospitalization and topiramate initiation (dose unknown), the patient had "9 hospital admissions for seizures and respiratory failure and had a long problem list." It is unknown whether topiramate therapy was continued and the event outcomes were not reported. Medical history included not reaching developmental milestones and scoliosis. Concomitant medications included phenobarbital, levetiracetam, pyridoxine, ranitidine, glycopyrronium, beclometasone dipropionate, salbutamol, clonazepam, and diazepam (all received for unknown times).

3.4.2 Summary of Events in Pediatric Patients < 2 Years of Age (N=18)

We identified 18 FAERS cases with topiramate in the pediatric population < 2 years of age (unlabeled patient population) reporting a serious outcome. A subset analysis of this patient population is presented in this section. Events of interest reported in all pediatric patients, including those < 2 years of age, have been discussed in the above sections. The DECs reported in these 18 cases were consistent with the known risks described in the labeling, or were disease or indication related. DECs reported in ≥ 3 cases included seizure, drug administered to inappropriate age, product use issue, and off label use.

Table 6 summarizes characteristics of the 18 pediatric FAERS cases of adverse events reported with topiramate in patients < 2 years of age for this case series.

Table 6. Characteristics of U.S. Pediatric Case Series for Patients < 2 Years of age With Topiramate (N=18)

Age	Mean	10.3 months
	Median	10.5 months
	Range	2 weeks – 23 months
Sex	Male	14
	Female	3
	Unknown	1
Report Year	2014	4
	2015	13
	2016	1
Reported Reason for Use*	Seizures/epilepsy	11
	Infantile spasms	6
	Lennox-Gastaut	1
Serious Outcome†	Death	1
	Life-threatening	0
	Hospitalized	7
	Disability	0
	Congenital anomaly	0
	Required Intervention	0
	Other serious	14

* Seizures/epilepsy use includes the following reported reasons for use: seizures, epilepsy, status epilepticus, myoclonic 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.

4 DISCUSSION

Drug utilization data show pediatric patients accounted for approximately 7% of the total patients who received a prescription for topiramate from outpatient retail pharmacies. Among all the pediatric age groups, the largest use of topiramate was in patients aged 12-17 years; however, use was seen in all the age groups examined.

Our review of the 76 FAERS cases with topiramate in the U.S. pediatric population demonstrated the majority of cases (58 of 76) were reported in pediatric patients ≥ 2 years of age. The most commonly reported reasons for use included seizures/epilepsy (51) and migraine prophylaxis (10).

Our review of the DECs reported in the 76 FAERS cases with topiramate in the U.S. pediatric population, including patients < 2 years of age (unlabeled patient population), 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 somnolence and fatigue, cognitive-related dysfunction (mental status changes, difficulty with concentration, memory, or speech), neuropsychiatric disturbances (aggression, abnormal/antisocial behavior, or depression), kidney stones, oligohidrosis and hyperthermia, myopia and secondary angle closure glaucoma, decreased appetite, weight loss, and insomnia. These adverse events are adequately described in the labeling, including several in Warnings and Precautions. In addition, the Sponsor has a post-market requirement to complete a one year prospective, randomized, controlled trial to evaluate the effects of topiramate as monotherapy for new-onset or recent-onset epilepsy on pediatric growth and maturation, bone mineral density, kidney stone formation, and cognitive and behavioral function in children 2 to 15 years of age (final report submission date anticipated September 2018).

Several unlabeled DECs were disease-related or indication-related, including seizure, drug ineffective, off label use, drug administered to patient of inappropriate age, condition aggravated, product substitution issue, product use issue, infantile spasms, and product quality issue. The cases reporting ineffective drug and product issues primarily reported seizures with the use of topiramate. 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. In addition, the use of multiple concomitant antiepileptics may result in a paradoxical increase in seizure activity or precipitation of other seizure types (Perruca, Gram, et al. 1998).

We identified three FAERS cases reporting death as an outcome with topiramate in the pediatric population, however, a causal association could not be established because of insufficient case details and consideration of underlying diseases and concomitant medications. Two cases were likely disease related, and reported death associated with either a respiratory infection or seizure. These two cases also reported several other concomitant antiepileptic medications. One case reported cardiac arrest and respiratory arrest secondary to an intentional suicide with ingestion of topiramate and did not contain sufficient case details for assessment. Topiramate is labeled for suicidal behavior and ideation (Topamax PI 2014).

We identified three FAERS cases reporting the unlabeled adverse events of anorexia nervosa (2) and bulimia nervosa (1) in the pediatric population. These three cases contained insufficient case details for causality assessment, including time to onset, dechallenge information, and concomitant medications. These cases also did not report baseline weights or heights for the patients; therefore, the clinical significance of the reported weight loss could not be assessed. In addition, these cases reported patient risk factors for developing eating disorders (e.g., history of eating disorders or depression). However, because of its potential to cause anorexia, weight decrease, and neuropsychiatric adverse events, the role of topiramate cannot be ruled out.

All three cases occurred in patient populations most commonly associated with anorexia nervosa or bulimia nervosa (i.e., adolescent females). All three cases reported adolescent aged females and reported other risk factors for anorexia nervosa or bulimia nervosa, including a family history of eating disorders, medical history of anorexia nervosa, or major depressive disorder (Fairburn and Harrison 2003). The lifetime prevalence of anorexia nervosa and bulimia nervosa are estimated to be 0.5-2% and 1-3%, respectively (Klein and Walsh 2004). Both conditions are most prevalent in adolescence and disproportionately affect females and males at a ratio of approximately 10:1 (Fairburn and Harrison 2003; Klein and Walsh 2004).

The association of topiramate with anorexia, weight decrease, and neuropsychiatric adverse events provides biologic plausibility supporting the possible association of topiramate with anorexia nervosa and bulimia nervosa. Topiramate is labeled for anorexia and weight decrease as some of the most common adverse reactions observed in adult and adolescent patients with epilepsy or migraines. Topiramate is also labeled for psychiatric or behavioral disturbances in both the epilepsy and migraine populations (Topamax PI 2014). Anorexia nervosa and bulimia nervosa are psychiatric disorders that involve the interaction of several genetic/biological, psychological, and socio-environmental risk factors (Klein and Walsh 2004; Balakar, Shank, et al. 2015).

The development of anorexia nervosa and bulimia nervosa in children and adolescents may have several detrimental effects. Research suggests that these eating disorders often co-occur with many psychiatric comorbidities including suicidality, and mood, anxiety, and conduct disorders (Balakar, Shank, et al. 2015; Klein and Attia 2016; Engel, Steffen, et al. 2016). These eating disorders may also be associated with several other medical complications, including amenorrhea, growth disturbances, cardiac abnormalities, hypotension, dehydration, and laboratory abnormalities (Klein and Attia 2016; Engel, Steffen, et al. 2016; Forman 2016). The two pediatric FAERS cases reporting anorexia nervosa also reported medical complications secondary to the eating disorder, including amenorrhea, cardiac abnormalities, and hypotension.

Topiramate in combination with phentermine (Qsymia) is approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults (Qsymia PI 2014). In addition, topiramate has been used off label for treatment of binge eating disorders, and studies have shown greater binge eating remission rates and greater weight loss with topiramate compared to placebo (Reas and Grilo 2015). Binge eating disorders are characterized by recurrent binge eating, but unlike anorexia nervosa and bulimia nervosa, there is the absence of weight compensatory behaviors (self-induced vomiting, laxative misuse, excessive exercise or

extreme restraint). We did not identify any FAERS cases reporting the use of topiramate for weight management or eating disorders in the 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. These serious unlabeled events included hypovolemic shock, acute kidney injury, cardiac arrest, respiratory arrest, and respiratory failure.

One case reported acute kidney injury and hypovolemic shock secondary to acute hepatic failure with topiramate. The events reported in this case (acute hepatic failure, hepatic encephalopathy, hyperammonemia, and acidosis) are consistent with the known risks described in the labeling for topiramate. Topiramate is labeled for hyperammonemia and encephalopathy and metabolic acidosis in the Warnings and Precautions section, and for hepatic failure (including fatalities) in the Postmarketing Adverse Reactions section. The pediatric migraine trials did not report any cases of hepatic failure or hepatic injury (Kapcala 2014). The adverse event of liver failure (including fatalities) was added to the Postmarketing Adverse Reactions section in 2002, and the Office of New Drugs (OND) does not consider hepatic failure to be clearly associated with topiramate. The Sponsor, OND, and DPV have been closely monitoring all reports of hepatic failure or hepatic injury with topiramate.

In addition, the long latency of 10 years reported in the case is not consistent with the typical onset of drug induced liver injury, but the role of topiramate cannot be ruled out because of a positive dechallenge response. Typically, the onset of drug induced liver injury is between 5 days and 3 months of starting a drug, but some drugs may have a longer latency of 3 to 12 months or years (LiverTox 2016).

One case reported cardiac arrest and respiratory arrest secondary to an intentional suicide with ingestion of topiramate and did not contain sufficient case details for assessment. Topiramate is also labeled for suicidal behavior and ideation. One case reported respiratory failure and seizures. This case lacked sufficient details for assessment, the events may have been disease related, and the case also reported several other concomitant antiepileptic medications.

5 CONCLUSION

We identified 76 FAERS cases with topiramate in the U.S. pediatric population reporting a serious outcome, including 3 deaths. Our evaluation of postmarketing adverse event reports does not suggest any new or unexpected pediatric safety concerns with topiramate at this time. We identified cases related to the unlabeled events of anorexia nervosa and bulimia nervosa and the labeled event of hepatic failure and will continue to monitor these as adverse events of interest in all patient populations.

6 RECOMMENDATIONS

DPV will continue routine pharmacovigilance for all pediatric adverse events associated with the use of topiramate, including anorexia nervosa, bulimia nervosa, and hepatic failure as adverse events of interest in all patient populations.

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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.

IMS Vector One®: Total Patient Tracker (TPT)

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 Vector One® 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. Vector One® receives over 2.1 billion prescription claims per year.

The patient estimates focus on only outpatient retail pharmacies; therefore, they may not be representative of utilization in other settings of care such as mail-order/specialty and non-retail settings.

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 PREFERRED TERMS

Designated Medical Event	MedDRA Preferred Terms (Version 18.1)
Acute pancreatitis	Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatic necrosis, Haemorrhagic necrotic pancreatitis
Acute respiratory failure	Acute respiratory failure, Respiratory failure, Acute respiratory distress syndrome
Agranulocytosis	Agranulocytosis, Neutropenia, Febrile neutropenia
Anaphylaxis and anaphylactoid reactions	Anaphylactic reaction, Anaphylactoid reaction, Anaphylactic shock, Anaphylactoid shock
Aplastic anemia	Aplastic anaemia, Bone marrow failure, Aplasia pure red cell
Blind	Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Sudden visual loss
Congenital anomalies	Congenital anomaly
Deaf	Deafness, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness bilateral, Deafness unilateral, Sudden hearing loss
Disseminated intravascular coagulation	Disseminated intravascular coagulation
Endotoxic shock, confirmed or suspected	Endotoxic shock, Septic shock
Hemolytic anemia	Haemolytic anaemia, Coombs positive haemolytic anaemia, Coombs negative haemolytic anaemia
Haemolysis	Haemolysis, Intravascular haemolysis, Haemoglobinaemia, Haemoglobinuria, Haptoglobin decreased
Liver failure	Hepatic failure, Hepatic encephalopathy, Acute hepatic failure, Subacute hepatic failure
Liver necrosis	Hepatic necrosis, Hepatitis fulminant, Hepatitis acute
Liver transplant	Liver transplant
Pancytopenia	Pancytopenia
Pulmonary fibrosis	Pulmonary fibrosis
Pulmonary hypertension	Pulmonary hypertension, Cor pulmonale
Renal failure	Acute kidney injury, Renal failure, Renal impairment
Rhabdomyolysis	Rhabdomyolysis
Seizure	Seizure, Epilepsy, Generalised tonic-clonic seizure
Stevens-Johnson syndrome	Stevens-Johnson syndrome, Erythema multiforme
Sudden death	Sudden death, Sudden cardiac death
Torsade de Pointes	Torsade de pointes
Toxic epidemal necrolysis	Toxic epidermal necrolysis, Dermatitis exfoliative
TTP	Thrombotic thrombocytopenic purpura
Ventricular fibrillation	Ventricular fibrillation
Suicide	Completed suicide
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome
ALS - Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Serotonin syndrome	Serotonin syndrome
Colitis ischaemic	Colitis ischaemic, Intestinal infarction
PML - 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

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=76)

FAERS Case #	Version #	Manufacturer Control #
11596490	1	US-JNJFOC-20150924527
11138725	1	PHHY2015US062564
10947110	2	US-JNJFOC-20140709882
10936799	2	US-JNJFOC-20140200988
10652537	2	US-MALLINCKRODT-T201404315
11459399	1	US-JNJFOC-20150808849
11459398	1	US-JNJFOC-20150808858
10937070	2	US-JNJFOC-20131019478
11459389	1	US-JNJFOC-20150808861
10937062	2	US-JNJFOC-20130914893
10563294	1	US-PFIZER INC-2014302829
10937130	2	US-JNJFOC-20141021540
10937196	2	US-JNJFOC-20130509743
10938891	2	US-JNJFOC-20130907808
11736114	1	US-JNJFOC-20150927541
10381127	1	FK201403078
12067186	1	US-JNJFOC-20160116381
10550073	2	US-LUNDBECK-DKLU1085167
11971093	1	Direct report
10936761	2	US-JNJFOC-20130907809
10042113	2	US-LUNDBECK-DKLU1096976
10573895	1	PHHY2014US140646
10936907	2	US-JNJFOC-20141006637

FAERS Case #	Version #	Manufacturer Control #
10543160	1	US-JNJFOC-20141013407
10936943	2	US-JNJFOC-20150214623
11065048	2	US-JNJFOC-20150320314
10868339	1	US-LUNDBECK-DKLU1109028
11590994	1	US-AUROBINDO-AUR-APL-2015-08832
11116199	1	Direct report
10930623	1	US-JNJFOC-20150309296
10936857	2	US-JNJFOC-20140719676
10470802	2	US-LUNDBECK-DKLU1103667
11819701	1	US-JNJFOC-20151118874
10218584	1	US-LUNDBECK-DKLU1100427
10896063	1	US-UCBSA-2015005669
10457556	1	PHHY2014US117136
10937146	2	US-JNJFOC-20150217719
11282124	2	PHEH2015US012973
11177964	1	Direct report
11141779 (duplicate)	1	Direct report
11828883	1	US-LUNDBECK-DKLU2007786
10162102	2	US-ELI_LILLY_AND_COMPANY-US201404009817
10255661 (duplicate)	2	US-JNJFOC-20140611479
10248666 (duplicate)	1	Direct report
10938890	2	US-JNJFOC-20130907807
10938900	2	US-JNJFOC-20140200985
10938889	2	US-JNJFOC-20130907806
11173837	2	UCM201505-000376
11138768 (duplicate)	1	PHHY2015US061717
11166686 (duplicate)	1	US-JNJFOC-20150510396
11220529 (duplicate)	1	US-LUPIN PHARMACEUTICALS INC.-2015-01587
11149665 (duplicate)	2	US-APOTEX-2015AP009574
10261366	1	US-LUPIN PHARMACEUTICALS INC.-2014-01118
10473964 (duplicate)	1	US-ACTAVIS-2014-20408
10936834 (duplicate)	2	US-JNJFOC-20140416098
11158977 (duplicate)	1	2014GMK009494
11230756 (duplicate)	1	2014AP003013
10938909	2	US-JNJFOC-20140401813
11279199	1	US-H14001-15-01177
11867720 (duplicate)	1	PHHY2015US166797
11293213 (duplicate)	4	US-SUPERNUS PHARMACEUTICALS, INC.-2015SUP00071
11873890 (duplicate)	1	US-APOTEX-2015AP015488
11197149 (duplicate)	1	US-JNJFOC-20150606842
11198422 (duplicate)	1	US-ACCORD-031508
11233915 (duplicate)	1	US-GLENMARK GENERICS (EUROPE) LTD-2015GMK017879
11890020 (duplicate)	1	US-TEVA-622556USA
11204191 (duplicate)	1	US-AUROBINDO-AUR-APL-2015-05211
10667198	1	Direct report
10037410	1	Direct report
10143332	1	Direct report
10132962	1	US-JNJFOC-20140411956
10728803	1	US-RANBAXY-2013US-66006
11369537	1	US-JNJFOC-20150700351
9999481	2	US-TEVA-391469USA

FAERS Case #	Version #	Manufacturer Control #
11457307	1	US-ACCORD-033425
11990404	2	US-MEDTRONIC-1047217
10476910	1	US-ACCORD-026080
10477306 (duplicate)	1	US-CIPLA LTD.-2014US01426
10547840 (duplicate)	1	US-RANBAXY-2014US-87084
10072469	1	2014P1002801
11089420	1	US-ACCORD-030403
11204913 (duplicate)	1	US-GLENMARK GENERICS (EUROPE) LTD-2015GMK017609
11789078 (duplicate)	1	US-TEVA-612829USA
11810158 (duplicate)	1	US-LUPIN PHARMACEUTICALS INC.-2015-03963
11084414 (duplicate)	1	US-AUROBINDO-AUR-APL-2015-03861
10269598	2	US-GLENMARK GENERICS INC.-2014GMK009904
10254234 (duplicate)	1	US-GLENMARK GENERICS (EUROPE) LTD-2014GMK009904
10055705	1	Direct report
10219602	1	Direct report
10208297	1	Direct report
10522863	1	ADR-2014-01858
10269386	2	US-DRREDDYS-USA/USA/14/0041373
10366942	1	2013SP006862
10938897 (duplicate)	2	US-JNJFOC-20130915208
10268079	1	Direct report
9998980	1	Direct report
10163052	2	PHHY2014US041059
10065345 (duplicate)	2	ADR-2014-00538
10395591	1	Direct report
10398868	1	2014SUP00025
10007467	1	US-TEVA-468386USA
10019073 (duplicate)	1	US-BRISTOL-MYERS SQUIBB COMPANY-20419206
10020797 (duplicate)	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2014SUN00555
9995519 (duplicate)	1	IMP_07488_2014
11089414	1	US-ACCORD-030405
11787866 (duplicate)	1	PHHY2015US153913
11204946 (duplicate)	1	US-GLENMARK GENERICS (EUROPE) LTD-2015GMK017611
11789157 (duplicate)	1	US-TEVA-612831USA
11084335 (duplicate)	1	US-AUROBINDO-AUR-APL-2015-03867
11089417	1	US-ACCORD-030402
12056714 (duplicate)	1	US-APOTEX-2015AP014969
11204907 (duplicate)	1	US-GLENMARK GENERICS (EUROPE) LTD-2015GMK017608
11789077 (duplicate)	1	US-TEVA-612828USA
11084407 (duplicate)	1	US-AUROBINDO-AUR-APL-2015-03859
10269387	2	US-DRREDDYS-USA/USA/14/0041354
11246197	1	US-CIPLA LTD.-2015US05286

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