Pediatric Focused Safety Review:

Topamax® (topiramate)

Pediatric Advisory Committee Meeting
September 23rd, 2011

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Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Background Information
- Pediatric Studies Supporting Labeling
- Additional Pediatric Labeling Changes July 2011
- Drug Use Trends
- Adverse Events: Fatal and Serious Nonfatal Outcomes
- Additional Relevant Safety Labeling
- Summary

Background Drug Information

- **Drug: Topamax® (topiramate)**
- **Formulations:**
  - Tablets: 25, 50, 100, and 200 mg
  - Sprinkle Capsules: 15 and 25 mg
- **Therapeutic Category:** anti-epileptic drug (AED)
- **Original Market Approval:** December 24th, 1996

Background Drug Information

- **Mechanisms of Action:** a sulfate substituted monosaccharide with unknown precise (MOA).
  - **Blocks voltage-dependent sodium channels**
  - **Augments** the activity of some **GABA-A receptors**
  - **Antagonizes the AMPA and kainate subtypes of the glutamate receptor**
  - **Inhibits** the enzyme **carbonic anhydrase**
  - **Modulates voltage-gated N and L type calcium ion channels.**

- **Sponsor: ORTHO MCNEIL JANSSEN**

Background Drug Information
Topamax® (topiramate)
Adult Indications

- Adjunctive treatment for partial onset seizures:
  - tablets: December 24th, 1996
  - capsules (sprinkles): October 16th, 1998
- Migraine prophylaxis: Aug 11th, 2004
- Monotherapy for partial onset and primary generalized seizures
  - August 29th, 2005

Background Drug Information
Topamax® (topiramate)
Pediatric Indications

- Adjunctive treatment for children 2-16 years:
  - partial onset seizures; July 23rd 1999

    Studies in 1-24 months, efficacy NOT established
  - generalized tonic clonic seizures; October 1st, 1999
- Treatment of children ≥ 2 years for seizures associated with Lennox-Gastaut syndrome; August 28th, 2001

Background Drug Information
Topamax® (topiramate)
Pediatric Indications -Continued

- Initial monotherapy for partial onset or primary generalized epilepsy in patients:
  - ≥ 10 years of age; June 29th, 2005
  - ≥ 2 years of age; July 15th, 2011

Background Information:
Studies to Support Pediatric Indications
Topamax® (topiramate)

- Adjunctive therapy for patients ≥ 2 years:
  - Randomized DB, PC, multicenter studies
  - Titration goal of 6 mg/kg/d
  - Maintenance period followed titration
- Monotherapy for partial onset or primary generalized seizures
  - 10 to15 years of age: 50 vs. 400 mg/d
  - 2 to < 10 years of age: pharmacometric bridging data used

PREA REQUIREMENT:
Studies to support Migraine Prophylaxis
Ages 12-17 Years

- Adult approval August 11th, 2004
- Final study report was submitted August 23rd, 2007
- No actual supplement was submitted by the Sponsor
- The Sponsor was not legally required to submit an efficacy or labeling supplement since the required study pre-dated the enactment of FDAAA legislation in September of 2007.
- Sponsor received a letter from the FDA in 2010, stating the PREA commitment was satisfied.
- **The product is not labeled for adolescents with migraine headaches**.
- A dose-related increase in serum creatinine, seen in adults, was also noted in patients aged 12-16 years.
  - Note: see use data regarding significant off-label use

Two Published Studies Migraine Prophylaxis Ages 12-17 Years

- "Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Topiramate for Migraine Prevention in Pediatric Subjects 12 to 17", Kurland et al., *Pediatrics,* 123;924, 2009.
- "Cognitive effects of topiramate in migraine patients aged 12 through 17 years," Pandina et al., *Pediatric Neurology,* 187: 187, 2010.

Topamax® (topiramate)
Outstanding PREA Requirements

- July 15th, 2011 (approved for monotherapy in 2 to < 10 years for epilepsy)
- Generated new PMR*
  - 1 year prospective randomized, parallel, active-control arm study to compare topiramate and comparator with regard to metabolic acidosis, renal stone formation, bone mineral density, and growth and development in patients 2-15 years of age.
  - Report submission due in September of 2018

*PMR = Post-marketing Requirement

BPCA Regulatory History
Topamax® (topiramate)

- **Written Request** (WR) issued July 9th, 2004
- **Indication:** adjunctive therapy for partial onset seizures with or without secondary generalization
- **Three studies (ages 1-24 months):**
  - Pharmacokinetic/Tolerability Study
  - Pediatric Safety and Efficacy Study
  - Pediatric 1 Year Safety Study
- **Pediatric Exclusivity** Granted July 24th, 2008
- **Pediatric Labeling change triggering safety review**: December 22nd, 2009
- **Labeling: Efficacy NOT demonstrated in this age group**

Patients with refractory partial onset seizures 1 to 24 months: Safety and Efficacy

- 55 patients open label PK/tolerability study
- 149 patients in a single double-blind, placebo-controlled, randomized study at doses of 5, 15, and 25 mg/kg/d over a 20 day period for safety and efficacy
- 284 patients participated in a 1 year open label safety extension study

Patients with refractory partial onset seizures 1 to 24 months -Continued:

- 34% had infantile spasms
- Mean age was 12 months
- **Safety and effectiveness as adjunctive therapy was not established**

Refractory partial onset seizures 1 to 24 months: Safety

- Increased risk of:
  - Infection (12% vs. 0% placebo)
  - Respiratory disorders (40% vs. 16% placebo)
- Dose related increased incidence of hyperammonemia
- Treatment for up to 1 year associated with reductions in Z scores for length, weight, and head circumference
- Increased impairment of adaptive behavior (no control for comparison)
- Increased mortality rate: 37 deaths/1000 patient years
- Background mortality rate for similar 1-24 month old patients is unknown

Labeling Changes
in July 2011 Topamax® (topiramate)
Section 1.1 Monotherapy Epilepsy

Table 2: Monotherapy Target Total Daily Maintenance Dosing for Patients 2 to <10 Years

Weight (kg)	Total Daily Dose (mg/day)* Minimum Maintenance Dose	Total Daily Dose (mg/day)* Maximum Maintenance Dose
Up to 11	150	250
12 - 22	200	300
23 - 31	200	350
32 - 38	250	350
Greater than 38	250	400

* Administered in two equally divided doses

Labeling 8.4 Pediatric Use
Adjunctive treatment for partial onset epilepsy in infants and toddlers (1-24 months); safety and efficacy not established

Labeling Changes in July 2011
5.11: Hypothermia with Concomitant Valproic Acid (VPA) Use

- **Drop in core body temperature to < 35°C (95°F)**
  - In the presence or absence of hyperammonemia
  - Warnings include lethargy, confusion, coma, and alterations in the cardiovascular or respiratory systems.

Additional Relevant Labeling: Risk Evaluation and Mitigation Strategy (REMS)

- **REMS approved April 23rd, 2009 and modified March 4th, 2011**
  - Suicidal ideation 2009 (Section 5.4; Medication Guide)
  - Cleft lip and/or cleft palate with in utero exposure 2011(Section 5.6; Medication Guide)
- **REMS discontinued June 27th, 2011**
  - Medication Guide as part of labeling adequately addresses public health risks (21 CFR 208.1)

Topamax® (topiramate) Use data

Topamax® (topiramate) Outpatient Utilization Data: CUMULATIVE USE April 2007 to March 2011

Source: SDI Vector One®: National and Total Patient Tracker

- Total population: 32.7 million prescriptions and 4.35 million patients
- **Pediatric population (0-16 years) accounted for 7% of total use: 2.1 million prescriptions and 315,000 patients**
  - **Majority of pediatric patients were aged 10-16 years (81% or 255,000 pediatric patients)**
  - Patients aged 0-1 year: 8,900 patients
  - Patients aged 2-9 years: 65,600 patients

Outpatient Utilization Data: Prescribing Specialties April 2007 to March 2011

Source: SDI Vector One®: National and Total Patient Tracker

Top prescribing specialties for topiramate by number of prescriptions dispensed from U.S. outpatient retail pharmacies, April 2007 - March 2011, cumulative

	Apr 07 - Mar 11	
	TRxs	Share%
Total Market	32,740,224	100.0%
Neurology	10,096,924	30.8%
GP/FM/DO	6,592,561	20.1%
Psychiatry	4,313,776	13.2%
Internal Medicine	3,624,435	11.1%
Unspecified	2,010,885	6.1%
Nurse Practitioner	1,665,966	5.1%
Physician Assistant	746,453	2.3%
Other	668,709	2.0%
Anesthesiology	546,044	1.7%
Pediatrics	**539,577**	**1.6%**
All Others	1,934,893	5.9%

Source: SDI Vector One®: National, Apr07-Mar11. Data Extracted Jun11.
File: VONA 2011-1218 topiramate MD 06-2011.xls
GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

Outpatient Utilization Data: Top Diagnoses by Patient Age as Reported by Office-Based Physicians April 2007 to March 2011

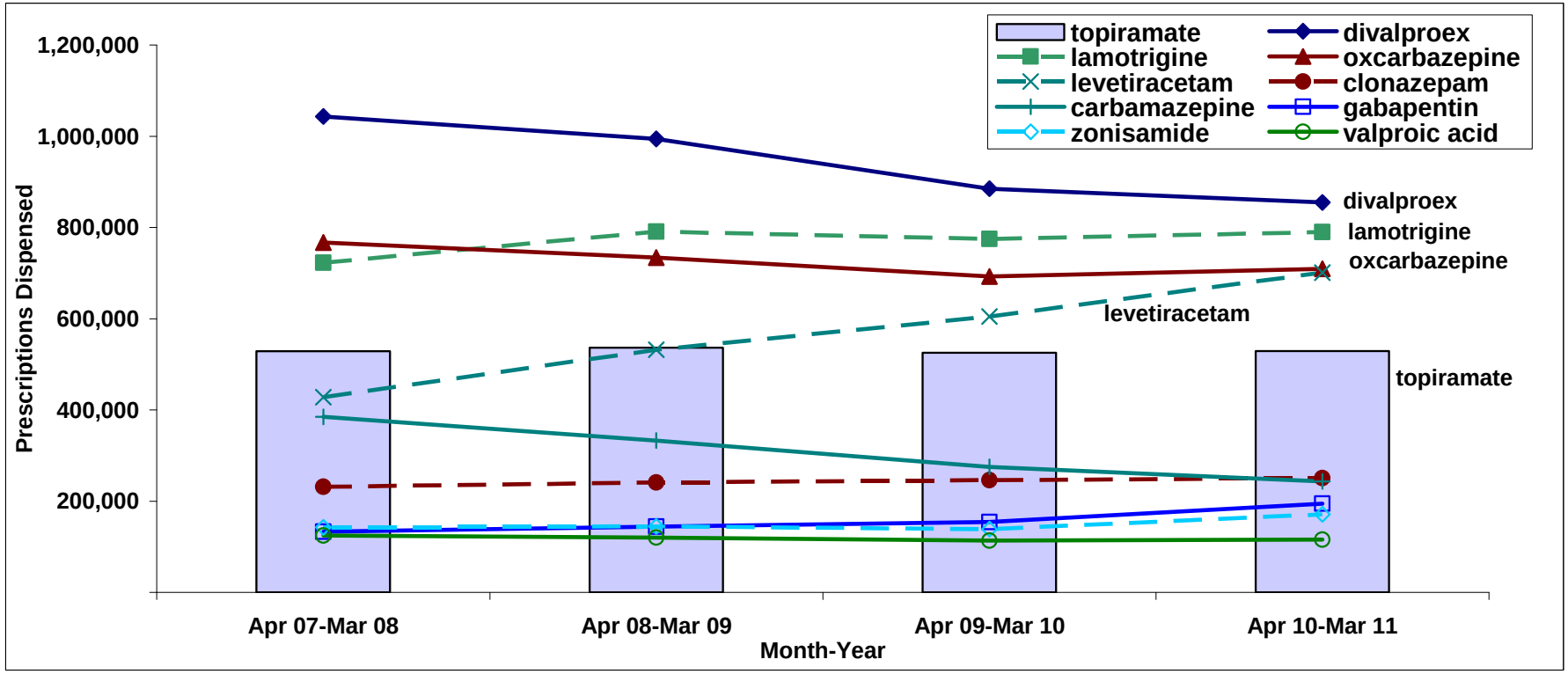
Source: SDI Vector One®: National and Total Patient Tracker

- Age 0-9 years: epilepsy, convulsions
- **Age 10-16 years: migraine, headache**
- Age 17+ years: migraine, headache

Note: headache and migraine are off-label uses in pediatric patients

Outpatient Utilization Data: Top 10 Seizure Medications April 2007–March 2008 to April 2010-March 2011

Projected number of prescriptions for the top 10 seizure disorder medications (USC class 20200) dispensed to the pediatric population (0-16 years) from U.S. retail pharmacies, April 2007 - March 2011



Source: SDI: Vector One®: National, Apr2007-Mar2011, Extracted June 2011. File: VONA 2011-1218 seizure disorders class 20200.xls

Topamax® (topiramate)
Pediatric Focused Safety Review

Crude Counts for Adverse Events since Initial Approval Topamax® (topiramate) December 24th, 1996 to March 31st, 2011

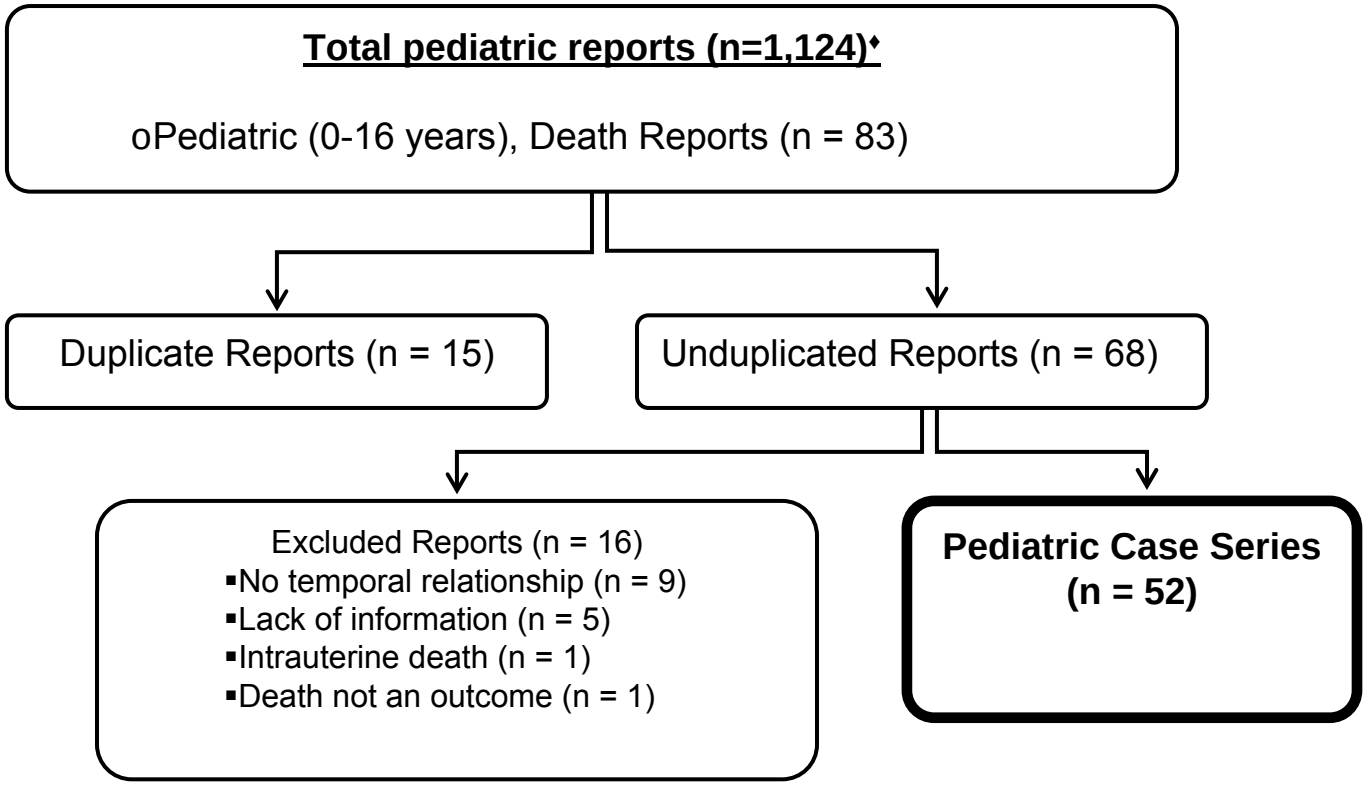
Table 1: Counts[1] of AERS Reports From December 24, 1996 to Data lock date March 31, 2011			
	All reports (US)[2]	Serious[3] (US)	Death (US)
Adults (≥ 17 yrs.)	5,504 (3,628)	2518 (1550)	582 (412)
Pediatrics (0-16 yrs.)	**1,124 (546)**	**581 (245)**	**83 (30)**
Age unknown (Null values)	1,829 (962)	697 (283)	117 (69)
Total	8,457 (5,136)	3,796 (2,078)	782 (511)

1 May include duplicates

2 US counts in parentheses

3 Serious adverse drug experiences include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly

Selection of Pediatric AERS cases with Death Outcome Topamax® (topiramate) December 24th, 1996 to March 31st, 2011



Pediatric Cases with Deaths (n=50, excluding 2 cases of fetal exposure)

- Gender: 26 male; 21 female
- Age: 2 months to 16 years (mean: 7 years)
- Dosing range: 12.5 - 600 mg (average: 140 mg)
- Duration of therapy: 6 days to 2 years (average: 178 days)
- Indications for use: seizure disorder (42)
- Concomitant medications (n=44): 1-10 range where information provided

Summary of Death Cases (n=50)*
Predominant Highlighted Features**

- Sudden Death (16)
- Hemorrhage (6)
- Hepatic or Renal Toxicity (6)
- Hyperthermia (6)
- Metabolic Acidosis (1)
- Suicide (2)
- Deaths from Status Epilepticus (1)
- ARDS (2)
- Miscellaneous (10)

*** Fetal deaths excluded (2)**

**** Unique cases were sorted based on a predominant clinical feature, although in many cases there were other features or overlapping features (e.g. status epilepticus and hyperthermia)**

SUDDEN DEATHS
(n = 16)
Examples

- 4 year old male asphyxiated following a seizure in his sleep (4 year old male; no other meds reported)
- 9 year old male who reportedly had a seizure, choked, and died in his sleep (also on phenytoin and vigabatrin)
- 7 year old female found dead possibly “from apnea due to nonconvulsive status epilepticus” (also on lamotrigine)
- 12 year old male who experienced respiratory arrest during an apparent witnessed seizure, followed by cardiac arrest (also on diazepam and lamotrigine)

5.8 Sudden Unexplained Death in Epilepsy

Hemorrhage (n = 6)

- 1 year old who developed a **severe nosebleed** 6 months after starting therapy with topiramate and died. No other information provided.
- 4 year old on valproic acid who started topiramate May 1999. She had severe abdominal pain and died. Autopsy showed cause of death as **hemorrhagic pancreatitis**.

Hemorrhage (n = 6)

- 5 year old male who began therapy with topiramate in April of 2005. In July of 2005 he experienced a **nosebleed**. Paramedics were unable to intubate because "**lungs were full of blood**."
- 3 year old male who started treatment August 11th, 2005, died of **pulmonary hemorrhage** in August, 2005.

Hemorrhage (n = 6)

- 9 year old female who initiated topiramate at an unknown date. The patient died acutely of **hemorrhagic pancreatitis** at an unspecified date. She took other unspecified AEDs.
- 6 year old female initiated topiramate 2006. At an unknown date presented with **bruising** all over the body, **thrombocytopenia, bone marrow depression, severe hemorrhage** and death.

Topamax July 15th, 2011 Label
Pediatric Adverse Events Associated with Bleeding

Type of Study	Population	Dosing	Adverse Event	% Incidence
Epilepsy Monotherapy	6 to < 16 Years	50 or 400 mg/day	Epistaxis	0% at 50 mg 4% at 400 mg
			Anemia	1% at 50 mg 3% at 400 mg;
			Intermenstrual Bleeding	0% at 50 mg 3% at 400 mg
Adjunctive Therapy for Epilepsy	2 to 16 years with Incidence ≥ 1%	N/A	Purpura	4% placebo; 8% Topamax
			Epistaxis	1 % placebo; 4 % Topamax
			Hematoma	0% placebo; 1 % Topamax
			Prothrombin increased; Thrombocytopenia	0% placebo; 1% Topamax
			Leukopenia	0% placebo; 2% Topamax

July 15th 2011 Label
Adult Adverse Events Associated with Bleeding

	Population	Dosing	Adverse Event	%
Adjunctive Therapy for Epilepsy	Adults with Incidence ≥ 1%	Placebo; 200-400 mg/day; 600-1000 mg/day	Epistaxis	1% placebo; 2% 400-600 mg; 1% 600-1000 mg
			Hematuria	1% placebo 2% 200-400 mg <1 % 600-1000 mg
			Menorrhagia	0% placebo 2% 200-400 mg 1% 600-1000
			Leukopenia	1% Placebo; 2% 400-600 mg; 1% 600-1000 mg

Other Adverse Events Associated with Bleeding Section 6: July 15th, 2011 Label

- **Platelet, Bleeding, and Clotting Disorders**: *Infrequent*: gingival bleeding, pulmonary embolism
- **Red Blood Cell Disorders**: *Frequent*: anemia; *Rare*: marrow depression, pancytopenia.
- **White cell and Reticuloendothelial System Disorders**: *Infrequent*: lymphadenopathy, eosiinophilia, lymphopenia, granulocytopenia. *Rare*: lymptocytosis.

Hemorrhage as Possible Safety Signal*

- 61 year old woman began topamax 25 mg/day for peripheral neuropathy.
- Experienced intractable epistaxis lasting 8 days. Epistaxis resolved 1 week following discontinuation.
- Topiramate was started 3 months later and epistaxis lasting 2 days ensued. She received 2 units of PRBCs.
- Concomitant medications: clopidogrel, aspirin, and prednisone. Patient was taking prednisone for > 1 year and all 3 medicines 3 months prior to exposure to topiramate.

* Scored 5 in favor of probable cause using the Naranjo Scale.

Page, R.L. and Bainbridge, J.L. Intractable Epistaxis Associated with Topiramate Administration. Ann Pharmacother 2006;40:1462-5.

Hemorrhage as Possible Safety Signal*

- 36 year old female with a history of anxiety/depression on 0.5 mg lorazepam qhs and 20 mg qd fluoxetine.
- Also history of diastolic hypertension and hypertension well-controlled on diet.
- For migraines she began taking 25 mg/day and this was gradually increased to 100 mg.

- Baseline blood chemistries showed no evidence of blood clotting abnormalities:
  - PT, PTT, fibrinogen, antithrombin III, Ast, Alt, Protein C and S.

* Scored 8 in favor of probable cause using the Naranjo Scale.

Page, R.L. and Bainbridge, J.L. Intractable Epistaxis Associated with Topiramate Administration. Ann Pharmacother 2006;40:1462-5.

Other Pediatric Safety Reports for Topamax

Hepatic or Renal Toxicity Examples (n = 6)

- 6 year old male with tuberous sclerosis who developed hepatorenal failure on an unknown date. Topiramate initiated March 1998 and patient died December 1998 of **hepatorenal syndrome**.
- 9 year old female with Rett's Syndrome initiated topiramate August 1999. **Hepatic enzymes and creatinine increased**. Seizures worsened and she died September 1999 secondary to "cardiovascular failure".

5.13 Adjustment of Dose in Renal Failure

5.14 Decreased Hepatic Function

5.25 Monitoring: Laboratory Tests

Hyperthermia
(n = 6)
Examples

- 4 year old male taken to the beach on a hot day, July 4th, 2002. He went into shock, suffered a cardiac arrest, with a rectal temperature of **106 degrees F**.
- 16 year old male initiated topiramate on an unknown date. He was found at home in July, 2003 with a body temperature of **110 degrees F.** He was hospitalized, cooled to 106 degrees, but died

5.2 Oligohidrosis and Hyperthermia

Suicide (n = 2)

- 16 year old female took an unknown amount of topiramate at an unknown time. EMS found her in cardiac arrest.
- 15 year old female took an unknown amount of topiramate, bupropion, clonidine, fluoxetine. No other information provided.

5.4 Suicidal Behavior and Ideation

Acute Respiratory Distress Syndrome (ARDS; n = 2)

- 4 year old female on 10 medications (including valproic acid and phenobarbital) started topiramate January 10th, 2008. She developed **ARDS while hospitalized** and expired in February, 2008.
- 12 year old female on valproic acid and clobazam, began taking topiramate at an unknown date. She was **hospitalized for pneumonapathy and developed ARDS,** which progressed to multi-organ failure. The patient died 12 hours following hospitalization and also had neutropenia.

6.4 and 6.5: adverse reactions observed during clinical trials

Metabolic Acidosis (n = 1)

- 8 month old male started treatment with topiramate November 6th, 2003. The patient developed a **metabolic acidosis with polypnea and renal failure**. The patient died in March, 2004 from an unspecified virus.

5.3 Metabolic acidosis

Status Epilepticus (n = 1)

- 3 year old male on valproic acid, carbamazepine, and clobazam, initiated topiramate December 12th, 2007. The patient **became ill and died in the hospital of status epilepticus**.

Miscellaneous Examples (n = 10)

- 8 year old female with protein losing gastroenteropathy, hypophosphatemia, and pulmonary obstruction. Cause of death reported as central respiratory failure. Concomitant medications included valproic acid, clobazam, baclofen, dimethicone, and lactulose.
- 1 year old on phenobarbital, valproic acid, nitrazepam, vigabatrin, and other medicines too numerous to list, started topiramate on an unknown date. There occurred an increase in the number of stomatocytes* in his blood and he died of respiratory insufficiency.

*hereditary deformation of red blood cells; swollen and cup shaped.

Crude Counts for Adverse Events since Pediatric Approval
December 22nd, 2009 to March 31st, 2011

Table 2: Counts[1] of AERS Reports
From December 22, 2009 to Data lock date March 31, 2011

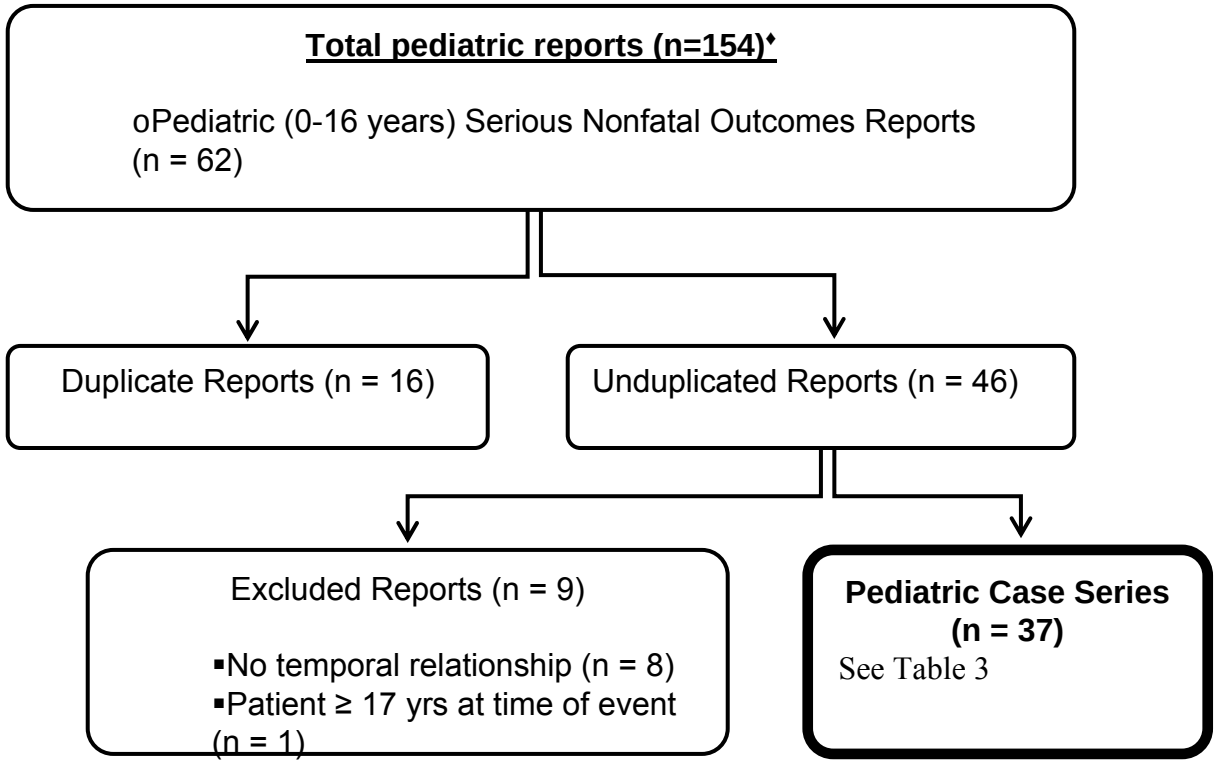
	All reports (US)[2]	Serious[3] (US)	Death (US)
Adults (≥ 17 yrs.)	1131 (638)	535 (316)	186 (150)
Pediatrics (0-16 yrs.)	**154 (42)**	**64 (15)**	**2 (0)**
Age unknown (Null values)	388 (170)	146 (41)	19 (12)
Total	1673 (850)	745 (372)	207 (162)

1 May include duplicates

[2] US counts in parentheses

3 Serious adverse drug experiences include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly

Case Characteristics
Serious Nonfatal Outcomes
December 22nd, 2009 to March 31st, 2011



Pediatric Cases with Nonfatal Serious Outcomes Continued (n=29)*

- Gender: 15 male; 14 female
- Age: mean 9 years; range 7 months to 16 years
- Dosing range: 15- 400 mg; avg. 130 mg.
- Duration of therapy: 1 day to 3 years; avg. 205 days
- Indications associated with use:
  - Seizure disorder (23)
  - Appetite suppression/weight loss (2)
  - Migraine prophylaxis (2)
- Outcome:
  - Hospitalization (25)
  - Other medically serious (15)
  - Life threatening (8)
  - Disability (1)

* 8 cases of fetal toxicity were excluded here

Pediatric Cases with Nonfatal Serious Outcomes (n=29)

- **Neuropsychiatric (3)**
  - Visual hallucinations, depersonalization, memory disturbance, agitation, psychosis, depersonalization, sensory disturbance
- **Drug interaction (3)**
  - Tic exacerbation, hyperammonemic encephalopathy, compensated metabolic acidosis.

Pediatric Cases with Nonfatal Serious Outcomes

- **Respiratory infection (2)**
  - URI; sore throat
- **Generic complaint/lack of effect (3)**
  - Muscle weakness; drug ineffective
- **Oligohydrosis/hypohydrosis (3)**
  - Also anhydrosis; hyperpyrexia

Pediatric Cases with Nonfatal Serious Outcomes

- **Miscellaneous (6)**
  - Overdose ,nephrocalcinosis, seizures, gastric ulcers, cholecystitis, increased amylase
- **Miscellaneous multiple events (9); <u>example</u>:**
  - Convulsions, pyrexia, incomprehensible speech and behavior, depressed level of consciousness with ocular deviation, liver disorder

Serious Nonfatal Cases
Examples of the Most Common SAE

- **Visual Hallucinations (3 nonduplicative):**
  - 14 year old female with tuberous sclerosis on topiramate 100 mg bid (also on oxcarbazepine) experienced psychosis and visual hallucinations that resolved with discontinuation of topiramate.
  - 10 year old male with subdural hematoma. Allergic to phenytoin so switched to topiramate 25 mg a day. The next day had visual hallucinations. The dose was increased slowly to 87.5 mg. Patient experienced excitement, irritability, and aggression. Other medications: VPA and zonisamide.
  - 16 year old female on topiramate 150 mg bid for epilepsy. Also taking clobazam and lamotrigine. She experienced visual hallucinations, depersonalization, sensory disturbance, and memory disturbance.

Topamax® (topiramate)
Additional Relevant Labeling

- 5.1: **Acute Myopia and Secondary Angle Closure Glaucoma**
  - Reversal of symptoms with discontinuation
- 5.2: **Oligohidrosis and Hyperthermia**
  - Majority of cases reported in pediatric patients
  - Pediatric patients should be monitored for decreased sweating and increased body temperature, especially in hot weather.
- 5.3: **Hyperchloremic, non-anion gap metabolic acidosis**
  - Serum bicarbonate below 10 meq/L noted
  - Associated with risk for nephrolithiasis, nephrocalcinosis, osteomalacia growth retardation
- 5.4: **Suicidal Behavior and Ideation**
  - Pooled analysis of clinical trials of 11 AEDs showed approximately two-fold increased risk of suicidal ideation.
  - Risk did not change with age.

Topamax® (topiramate) Additional Relevant Labeling (continued)

- 5.5: **Cognitive/Neuropsychiatric Adverse Reactions:**
  - Psychomotor slowing including: difficulty with concentration/attention, speech and language problems, headache, dizziness, anorexia, and somnolence.
- 5.6: **Fetal Toxicity**
  - Infants exposed in utero have an increased risk of cleft lip and/or cleft palate (oral clefts).
- 5.7: **Withdrawal of Antiepileptic Drugs (AEDs)**
  - Gradual withdrawal to avoid seizures

Topamax® (topiramate) Additional Relevant Labeling

- 5.8: **Sudden Unexplained Death in Epilepsy (SUDEP)**
  - 10 deaths in 2796 years of patient exposure; within range for patients with epilepsy not taking topamax
- 5.9: **Hyperammonemia and Encephalopathy (With or Without Concomitant Valproic Acid (VPA) Therapy**
  - Seen in patients 12-16 years of age treated with topiramate monotherapy for migraines (unapproved); 22% placebo versus 41% 100 mg/day
  - Hyperammonemia occurred with and without encephalopathy.
  - Hyperammonemia occurs more often when topiramate is given concomitantly with valproic acid.
  - Signs and symptoms usually abate with discontinuation of either drug.

Topamax® (topiramate) Additional Relevant Labeling

- 5.9: **Hyperammonemia and Encephalopathy (With or Without Concomitant Valproic Acid (VPA) Therapy (continued)**
  - Patients with inborn errors of metabolism including mitochondrial disorders may be at increased risk for hyperammonemia.
  - Monitor ammonia levels where there is lethargy, change in mental status, or vomiting.
- 5.10: **Kidney Stones**
  - Up to 1 year exposure in study of 284 pediatric patients 1-24 months old with epilepsy had a 7% incidence of kidney or bladder stones diagnosed clinically or by sonogram.

Topamax® (topiramate)
Additional Relevant Labeling

- 5.12: **Paresthesia**
  - Usually tingling of extremities: more often reported in monotherapy for epilepsy and migraine prophylaxis
- 5.13: **Adjustment of Dose in Renal Failure**
  - May be necessary in patients with renal compromise
- 5.14: **Decreased Hepatic Function**
  - Administer with caution as clearance may be decreased.

Topamax® (topiramate)
Additional Relevant Labeling

5.15: **Monitoring with Laboratory Tests**:

- A non-anion gap, hyperchloremic metabolic acidosis manifests as a decrease in serum bicarbonate and an increase in serum chloride.
- Measure baseline and periodic serum bicarbonate and chloride.
- In patients 12-16 years treated for migraine (off label); dose-related increase in serum creatinine
- In patients < 2 years (off label):
  - Increased creatinine, BUN, alkaline phosphatase, total protein, total eosinophil count, and decreased potassium

Summary Pediatric Focused Safety Review Topamax® (topiramate)

- This concludes the pediatric focused safety review.
- The FDA will continue to monitor for any new bleeding events
- Does the Committee concur?

ACKNOWLEDGEMENTS

OND

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