Pediatric Focused Safety Review:
Topamax® (topiramate)

Pediatric Advisory Committee Meeting
September 23rd, 2011

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Pediatric and Maternal Health Staff
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 24\textsuperscript{th}, 1996
  - capsules (sprinkles): October 16\textsuperscript{th}, 1998
- Migraine prophylaxis: Aug 11\textsuperscript{th}, 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 to 15 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.

Topamax® (topiramate)
Outstanding PREA Requirements

- July 15\textsuperscript{th}, 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

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

* 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 $< 35^\circ\text{C} (95^\circ\text{F})$
  - 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

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


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

Topamax® (topiramate)
Pediatric Focused Safety Review
Table 1: Counts\(^1\) of AERS Reports
From December 24, 1996 to Data lock date March 31, 2011

<table>
<thead>
<tr>
<th>Age Group</th>
<th>All reports (US)(^2)</th>
<th>Serious(^3) (US)</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 yrs.)</td>
<td>5,504 (3,628)</td>
<td>2518 (1550)</td>
<td>582 (412)</td>
</tr>
<tr>
<td>Pediatrics (0–16 yrs.)</td>
<td>1,124 (546)</td>
<td>581 (245)</td>
<td>83 (30)</td>
</tr>
<tr>
<td>Age unknown (Null values)</td>
<td>1,829 (962)</td>
<td>697 (283)</td>
<td>117 (69)</td>
</tr>
<tr>
<td>Total</td>
<td>8,457 (5,136)</td>
<td>3,796 (2,078)</td>
<td>782 (511)</td>
</tr>
</tbody>
</table>

\(^1\) 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

Total pediatric reports (n=1,124)*
- Pediatric (0-16 years), Death Reports (n = 83)

Duplicate Reports (n = 15)
Unduplicated Reports (n = 68)

Excluded Reports (n = 16)
- No temporal relationship (n = 9)
- Lack of information (n = 5)
- Intrauterine death (n = 1)
- Death not an outcome (n = 1)

Pediatric Case Series (n = 52)
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.
### Pediatric Adverse Events Associated with Bleeding

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

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33
## July 15th 2011 Label
### Adult Adverse Events Associated with Bleeding

<table>
<thead>
<tr>
<th>Population</th>
<th>Dosing</th>
<th>Adverse Event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunctive Therapy for Epilepsy</td>
<td>Adults with Incidence ≥ 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo; 200-400 mg/day; 600-1000 mg/day</td>
<td>Epistaxis</td>
<td>1% placebo; 2% 400-600 mg; 1% 600-1000 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematuria</td>
<td>1% placebo 2% 200-400 mg &lt;1% 600-1000 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Menorrhagia</td>
<td>0% placebo 2% 200-400 mg 1% 600-1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukopenia</td>
<td>1% Placebo; 2% 400-600 mg; 1% 600-1000 mg</td>
</tr>
</tbody>
</table>
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, eosinophilia, 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.

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.

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 4\textsuperscript{th}, 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 10\textsuperscript{th}, 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 pneumonopathy 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 6\textsuperscript{th}, 2003. The patient developed a \textit{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 12\textsuperscript{th}, 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 22\textsuperscript{nd}, 2009 to March 31\textsuperscript{st}, 2011

<table>
<thead>
<tr>
<th>Age Group</th>
<th>All reports (US)\textsuperscript{2}</th>
<th>Serious\textsuperscript{3 (US)}</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (\geq 17 yrs.)</td>
<td>1131 (638)</td>
<td>535 (316)</td>
<td>186 (150)</td>
</tr>
<tr>
<td>Pediatrics (0-16 yrs.)</td>
<td>154 (42)</td>
<td>64 (15)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Age unknown (Null values)</td>
<td>388 (170)</td>
<td>146 (41)</td>
<td>19 (12)</td>
</tr>
<tr>
<td>Total</td>
<td>1673 (850)</td>
<td>745 (372)</td>
<td>207 (162)</td>
</tr>
</tbody>
</table>

\textsuperscript{1} May include duplicates
\textsuperscript{2} US counts in parentheses
\textsuperscript{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 22\textsuperscript{nd}, 2009 to March 31\textsuperscript{st}, 2011

**Total pediatric reports (n=154)*

- Pediatric (0-16 years) Serious Nonfatal Outcomes Reports (n = 62)

**Duplicate Reports (n = 16)**

**Unduplicated Reports (n = 46)**

**Excluded Reports (n = 9)**
- No temporal relationship (n = 8)
- Patient ≥ 17 yrs at time of event (n = 1)

**Pediatric Case Series (n = 37)**
See Table 3
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, hyperammononemic 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); example:**
  – 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 topamox

• 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.
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?
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