Pediatric Focused Safety Review
Topamax (topiramate)
Pediatric Advisory Committee Meeting
September 14, 2016

Mona Khurana, M. D.

Division of Pediatric and Maternal Health
Office of New Drugs

Center for Drug Evaluation and Research

Food and Drug Administration

Outline

- Background Information
- Relevant Safety Labeling
- Pediatric Studies
- Pediatric Labeling Changes
- Drug Use Trends
- Adverse Events
- Summary

Background Information
Topamax (topiramate)

Drug:	Topamax (topiramate)
Formulation:	Oral tablets
	(25 mg, 50 mg, 100 mg, 200 mg)
	Oral sprinkle capsules
	(15 mg, 25 mg)
Drug Class:	Anti-Epileptic
Sponsor:	Janssen Pharmaceuticals, Inc.

Background Information: Topamax (topiramate)

U.S. Approval History Of Topamax (topiramate)	
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 2 years to 16 years of age
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 and older
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 and older
7/15/2011	Initial monotherapy for partial onset or primary generalized tonic-clonic seizures in patients 2 years of age and older
3/28/2014	***Prophylaxis for migraine headache in patients 12 years of age and older***

Relevant Safety Labeling: Topamax (topiramate)

Section 5 Warnings and Precautions

5.1 Acute Myopia and Secondary Angle Closure Glaucoma
5.2 Visual Field Defects
5.3 Oligohidrosis and Hyperthermia
5.4 Metabolic Acidosis
5.5 Suicidal Behavior and Ideation
5.6 Cognitive/Neuropsychiatric Adverse Reactions
5.7 Fetal Toxicity
5.8 Withdrawal of Antiepileptic Drugs (AEDs)

Relevant Safety Labeling: Topamax (topiramate)

Section 5 Warnings and Precautions

5.9 Sudden Unexplained Death in Epilepsy (SUDEP)

5.10 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)

5.11 Kidney Stones

5.12 Hypothermia with Concomitant Valproic Acid (VPA) Use

5.13 Paresthesia

5.14 Adjustment of Dose in Renal Failure

5.15 Decreased Hepatic Function

5.16 Monitoring: Laboratory Tests

Pediatric Studies: Topamax (topiramate)

- Multi-center, randomized, 16-week double-blind treatment phase, parallel-group trial comparing safety, efficacy, and tolerability of Topamax 50 mg/day and 100 mg/day to placebo for episodic migraine prophylaxis with or without aura (ages 12 to 17 years, n=103; 39% male)
  - 100 mg Topamax dose showed 28% greater mean reduction from baseline than placebo in monthly migraine attack rate (p=0.0164)

Pediatric Studies: Topamax (topiramate)

- Long-term safety based on 219 adolescent patients
  - 20-week, flexible-dose (2-3 mg/kg/day) placebo controlled study (6 to 16 years including 67 adolescents; n=157)
  - Open-label extension phases from 3 studies of migraine prophylaxis in adults that included 49 adolescents

Pediatric Studies: Topamax (topiramate)

- Adverse reactions in adolescent migraine patients generally similar to Topamax's known and labeled safety profile in pediatric patients and adults treated for other indications but notable changes included:
- ***Changes in baseline pulse and blood pressure**** more common in Topamax- vs. placebo-treated adolescents with migraine
- Most frequent laboratory abnormalities
  - Metabolic acidosis (low serum bicarbonate)
  - Increased creatinine, urea, ***uric acid****, chloride, ammonia, total protein, platelets and decreased serum phosphorus

*Newly incorporated into Topamax labeling

Pediatric Labeling Changes: Topamax (topiramate)

8.4 Pediatric Use

- Efficacy of topiramate for migraine prophylaxis in adolescents is demonstrated for a 100 mg daily dose *[see Clinical Studies (14.3)]*
- Most commonly observed adverse reactions were paresthesia, upper respiratory tract infection, anorexia, and abdominal pain *[see Adverse Reactions (6)]*
- Most common cognitive adverse reaction was difficulty with concentration/attention *[see Warnings and Precautions (5.6)]*

Pediatric Labeling Changes: Topamax (topiramate)

8.4 Pediatric Use

- Markedly abnormally low serum bicarbonate values indicative of metabolic acidosis were reported in topiramate-treated adolescent migraine patients *[see Warnings and Precautions (5.4)]*
- Abnormally increased results were more frequent for creatinine, BUN, uric acid, chloride, ammonia, total protein, and platelets. Abnormally decreased results were observed with topiramate vs placebo treatment for phosphorus and bicarbonate *[see Warnings and Precautions (5.16)]*

Pediatric Labeling Changes: Topamax (topiramate)

8.4 Pediatric Use

- Notable changes (increases and decreases) from baseline in systolic blood pressure, diastolic blood pressure, and pulse were observed occurred more commonly in adolescents treated with topiramate compared to adolescents treated with placebo *[see Clinical Pharmacology (12.2)]*
- Safety and effectiveness in pediatric patients below the age of 12 years have not been established for the prophylaxis treatment of migraine headache

Drug Utilization Data: Topamax (topiramate)

Nationally estimated number of pediatric patients with a dispensed prescription for topiramate from U.S. outpatient retail pharmacies

	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
Note: Unique patient counts may not be added due to possibility of aging process during the study

Adverse Events: Topamax (topiramate)

(March 1, 2014* - February 29, 2016)

	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)§

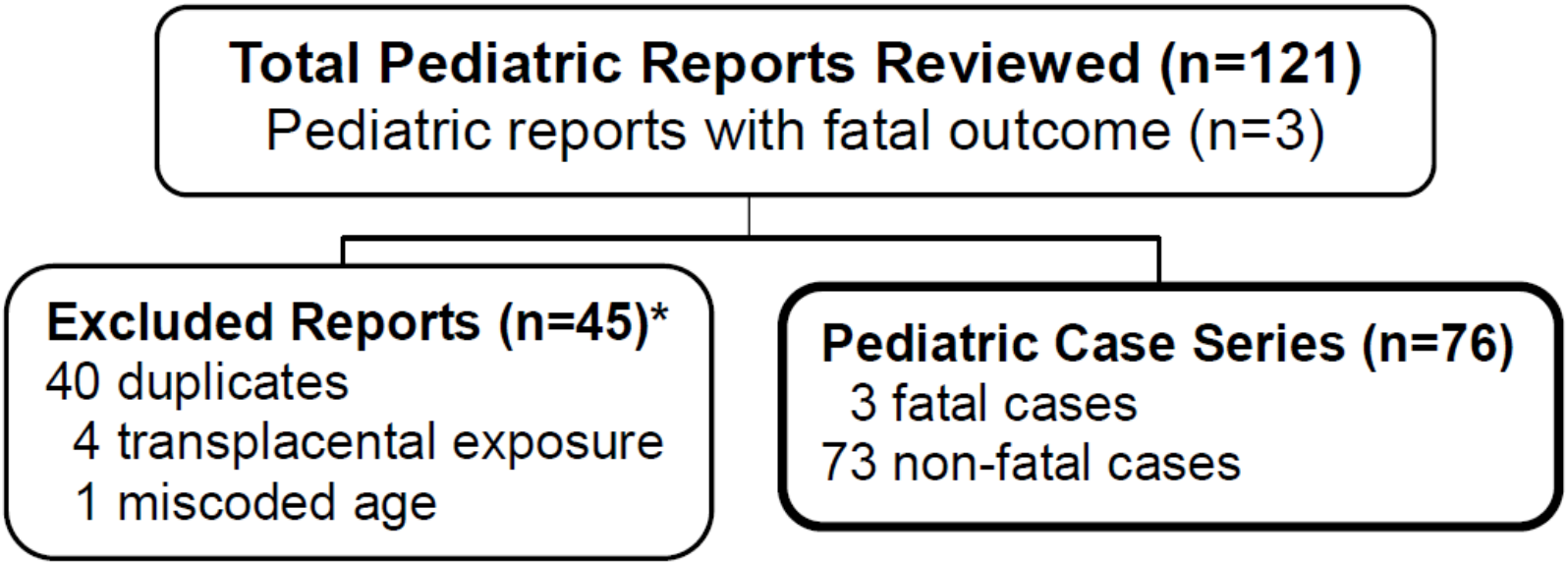
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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

§ One report of U.S. pediatric death was identified among reports not reporting an age

Adverse Events: Topamax (topiramate)

Selection of Pediatric FAERS Cases



* Reviewed prior to exclusion

Adverse Events:
Topamax (topiramate)

Summary of Fatal Cases (n=3)

- A 13 month old boy with multifocal complex partial seizures, occasionally associated with apnea and respiratory infection, on a ketogenic diet for refractory seizures died after developing a respiratory infection
- A 3 year old boy taking topiramate, levetiracetam, and lorazepam for epilepsy experienced a seizure and died
- A 16 year old of unknown sex committed suicide by ingestion of an unknown amount of topiramate

Adverse Events: Topamax (topiramate)

Serious Labeled Drug Event Combinations

- Reported in 3 or more cases
  - Somnolence and fatigue
  - Cognitive-related dysfunction
  - Neuropsychiatric disturbances
  - Kidney stones
  - Oligohidrosis and hyperthermia
  - Myopia and secondary angle closure glaucoma
  - Decreased appetite and weight loss
  - Insomnia

Adverse Events:
Topamax (topiramate)

Serious Unlabeled Drug Event Combinations

- Anorexia nervosa (n=2)
- Bulimia nervosa (n=1)
- Cardiac Arrest, Respiratory Arrest due to Suicide* (n=1)
- Acute Kidney Injury and Hypovolemic Shock due to Acute Hepatic Failure* (n=1)
- Respiratory Failure (n=1)

* Suicidal behavior and ideation and acute hepatic failure are labeled events

Previous PAC Discussion: Topamax (topiramate)

- September 22, 2011
  - Revise labeling to better define weight loss, bone mineralization, and life-threatening nature of some episodes of epistaxis in pediatric patients
- September 19-20, 2013
  - FDA stated post-market safety study under development intended to explore potential associations with nephrolithiasis, growth, cognitive function, and bone effects
  - PAC recommended tracking serious and non-serious cognitive adverse effects

PREA Post-Marketing Requirement (PMR): Topamax (topiramate)

- Issued with 2011 approval for expanded pediatric use for monotherapy of partial epilepsy
  - A 1 year prospective randomized, parallel, active-control arm study to compare topiramate and comparator with regard to metabolic acidosis, renal stone formation, decreased bone mineral density, growth retardation, and delayed sexual development in patients 2 years to 15 years of age
  - Final study report due: September, 2018

Summary:
Topamax (topiramate)

- This concludes the pediatric focused safety review
- No new pediatric safety signals were identified
- Plan to monitor for anorexia nervosa, bulimia nervosa, and acute hepatic failure in all patient populations
- FDA recommends continuing ongoing surveillance
- FDA will review PREA PMR once submitted
- Does the Committee concur?

ACKNOWLEDGEMENTS

Division of Neurology Products
Heather Fitter, MD
Norman Hershkowitz, MD PhD
Leonard Kapcala, MD

Division of Pediatric and Maternal Health
John J. Alexander, MD MPH
Ethan D. Hausman, MD
Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD
Lynne Yao, MD

Office of Pediatric Therapeutics
Judith U. Cope, MD MPH
Robert 'Skip' Nelson, MD PhD
Amy Odegaard, MPH
LCDR Kenneth Quinto, MD MPH
Pam Weinel, MS MBA RN

OSE
Grace Chai, PharmD
Corrinne Kulick, PharmD BCNSP
Joann H. Lee, PharmD
Robert L. Levin, MD
Karen Long, PharmD
Travis Ready, PharmD