



# Topamax and Birth Defects

Contact Jim Ronca, Esquire

Email:  
jronca@anapolschwartz.com  
Toll Free: (866) 735-2792

Read more information online at:  
[www.anapolschwartz.com](http://www.anapolschwartz.com)

© 2011 All Rights Reserved.

**MEDICAL DISCLAIMER:** This PDF is not designed to and does not provide medical advice, professional diagnosis, opinion, treatment or services or otherwise engage in the practice of medicine, to you or to any other individual. Please use this information to help in your conversation with your physician. This is general information and always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition. Never disregard or delay seeking professional medical advice or treatment because of content found in the PDF, website, or newsletter.

## CONTENTS

Epilepsy and Pregnancy	2
Anti-epileptic drugs (AEDs) in pregnancy and Teratogenicity	2
Topamax: Mechanism of action, pharmacology and related effects	2
Pre-Market Animal studies	3
Human Studies of Topamax in Pregnancy	3
Detailed Review	3
Topamax Approval History NDA 020505	17

**ATTORNEY DISCLAIMER:** This PDF is dedicated to providing general public information regarding legal rights. None of the information on this PDF is intended to be formal legal advice, nor the formation of a lawyer or attorney client relationship. Please contact a Lawyer for information regarding your particular case. This PDF is not intended to solicit clients outside the states of Pennsylvania, New Jersey, Ohio, West Virginia and Arizona.



Topamax (generic topiramate) is an anti-seizure medication also used to prevent migraine headaches. Topamax has been used off-label to treat mood instability, eating disorders and other psychiatric disorders. As with all anti-epileptic drugs (AEDs) there have been concerns about possible teratogenicity. On March 4, 2011, The FDA released a new MedAlert safety Update changing Topamax from a Pregnancy C to a Pregnancy D category and adding a [warning about pregnancy](#).

## **EPILEPSY AND PREGNANCY**

Most women with epilepsy have normal babies, however, seizures during pregnancy can cause harm to the unborn baby. Very rarely, grand mal seizures or generalized tonic-clonic seizures can cause miscarriages. However, grand mal seizures alone have not been associated with malformations or birth defects.

## **ANTI-EPILEPTIC DRUGS (AEDS) IN PREGNANCY AND TERATOGENICITY**

Congenital malformations have been reported with use of all AEDs. A prospective international study comparing babies exposed to AEDs with those having no exposure found a 3-1 increased risk of malformations. The incidence increased with (1) polytherapy (multiple AEDs at the same time) and (2) increased dose. Offspring of women taking AEDs have an increased frequency of both major and minor congenital abnormalities. Major anomalies include neural tube defects (such as spina bifida), cardiac defects, microcephaly, cleft lip/cleft palate, urogenital anomaly and developmental delay. Minor anomalies include craniofacial anomalies, digital anomaly and hypoplasia. The specific mechanism is unknown and likely multi-factorial. The general rate for congenital malformations after AED exposure is 4 to 8% which is about twice the general population. Polytherapy increases the risk so the general guideline for therapy during pregnancy has been monotherapy, if possible at the lowest effective dose for seizure. As to migraine prevention, guidelines have not been generally established. All AEDs are currently labeled Pregnancy category C or D. For a description of the FDA categories A through D see attached.

## **TOPAMAX: MECHANISM OF ACTION, PHARMACOLOGY AND RELATED EFFECTS.**

Topamax (topiramate) is considered one of the “newer” AEDs and is structurally unrelated to other anti-convulsive medications. Its true mechanism of action is unknown. Topamax is believed to suppress or prevent abnormal activity of the nerves in the brain that cause seizures and may prevent the abnormal activity from spreading to other nerves. Because Topamax may cause metabolic acidosis which may cause decreased fetal oxygenation, pregnant women taking Topamax have been cautioned to be monitored for metabolic acidosis throughout pregnancy. Unfortunately, the effect of topiramate caused metabolic acidosis in pregnancy has not been well studied.



Topamax is rapidly absorbed in about 2 hours and has 80% bioavailability. Its half life is 20 to 30 hours. It is excreted primarily through the urine in an unaltered state.

## **Birth control agents are less effective in the presence of Topamax.**

### **PRE-MARKET ANIMAL STUDIES**

Topamax showed developmental toxicity in preclinical studies of mice, rats and rabbits. In mice, malformations occurred at all tested doses, the lowest of which was 20% of the human dose. Craniofacial malformations were the most commonly observed. In rats, reduced fetal body weight occurred at doses 20% of human dose with limb reduction occurring at 10 times human dose. In rabbits, an increase in intrauterine death occurred at twice human dose and skeletal abnormalities at 6 times human dose. It should be noted that we do not know the nature or severity of these “abnormalities.”

### **HUMAN STUDIES OF TOPAMAX IN PREGNANCY**

Pre-marketing trial had 8 exposed pregnancies. Five were electively aborted and the other 3 resulted in normal infants. In 1998, there was a case report of an infant born to a mother on Topamax with multiple minor abnormalities. Cases of hypospadias in male infants are cited without detail in the product label and in a personal communication summarizing Finnish data. (Yerby 2003)



### **DETAILED REVIEW**

#### **A. Cleft Lip and Palate—General discussion<sup>1</sup>**

1. Cleft lip with or without cleft palate is one of the most common structural birth defects.
2. CL/CP varies from small notches in the lip to clefts that extend through the alveolar ridge in the maxilla and involve the floor of the nostril/palate. Treatments include multiple surgeries, speech therapy, dental and orthodontic treatments over the first 18 years of life.
3. Costs of this treatment is in the hundreds of thousands of dollars.
4. Providing care goes beyond just the treatment. Families and caregivers must be educated in how to deal with cleft lip/palate issues (e.g. emotional issues to special feeding bottle).

<sup>1</sup> P. Bender, Genetics of Cleft Lip and Palate, Journal of Pediatric Nursing 15:4 p242 (August 2000)



5. Approximately 30,000 children are born to epileptic mothers each year. D. Hill, Teratogenic effects of antiepileptic drugs, *Expert Rev Neurother*. 2010 June; 10(6):943-959. There are many more births to women using Topamax for migraine prophylaxis and off-label uses. There are no easily available numbers for these exposures.
6. Lip and palate development

Clefts of the lip are the result of the failure to merge of the lateral nasal and median nasal processes, part of the frontonasal prominence, and the maxillary prominence. Closure of the lip is normally completed by the 35th day of embryonic development. Any factor that disrupts the normal embryonic facial development could result in CL/CP.

- a. During the third week of gestation neural crest cells proliferate and begin to migrate into the front nasal and arch regions to form the 5 facial primordials (small buds of tissue)
- b. By the beginning of the 4th week, the five primordials form consisting of the frontonasal prominence (which forms the forehead and nose), two maxillary prominences (which forms the primitive mouth), and two mandibular prominences (which also forms part of the primitive mouth).
- c. During the 4th week, the medial ends of the mandibular prominence join to form the mandible, lower lip and lower cheek.
- d. Toward the end of the 4th week, the nostrils begin to form
- e. The upper lip is forms in the 6th and 7th week.
- f. Palate development begins in the 5th week and is complete at the end of the 12th week.
- g. Fusion of the hard palate is completed by the 10th week
- h. Development of the soft palate and the uvula is complete by the 12th week. Classification

Cleft classification is based on embryologic development and is defined by the cause and the extent of physical involvement. Category causes include: (1) nonsyndromic CL/CP, (2) nonsyndromic CP, (3) syndromic CL/CP, and (4) syndromic CP (Schutte & Murray, 1999). Nonsyndromic is defined as no physical or development anomalies except the CL/CP and no known teratogenic exposures that cause CL/CP. When CL/CP are described by the extent of the tissue involvement, they are unilateral or bilateral, and incomplete or complete. CL/CP involving only one side of the face are unilateral and when both sides are involved they are bilateral.

## 7. Incidence

Nonsyndromic CL/CP occurs in about 1/700 newborns. Native Americans have the highest incidence (3.6/1000) followed by Japanese (2.1) Chinese (1.7) and Caucasian (1.0). African Americans have the lowest (0.3). Left unilateral are most frequent, followed by right and bilateral 6:3:1. About 70% of unilateral and 85% of bilateral clefts involve the palate.

8. Cause in the general population is poorly understood and it is generally recognized that the etiology is multifactoral involving heredity and environment.<sup>2</sup> CL/CP has been associated with maternal alcohol use<sup>3</sup>, maternal cigarette

<sup>2</sup> Wyszynski, d; Mitchell, L; Report of Newly formed International Consortium for Oral Cleft Genetics; *Cleft Palate-Craniofacial Journal*; 1999;36:174-178

<sup>3</sup> Hassler, J.A., & Moran, D.J. (1986). Effects of ethanol on the cytoskeleton of migrating and differentiating neural crest cells: Possible role in teratogenesis. *Journal of Craniofacial Genetics Developmental Biology*, 6(2S), 129-136.



smoking<sup>4</sup> and maternal nutrition<sup>5</sup> There are several known teratogens, substance that causes a birth defect, that increase the risk for CL/CP. These include antiepileptic drugs (phenytoin, valproic acid), thalidomide, dioxin (pesticide), and retinoic acid.

## B. Pregnancy in women with epilepsy

1. Women who have epilepsy and become pregnant likely are taking anti epileptic drugs (AED).
2. In 2002 it was estimated that 1 million women with epilepsy were of childbearing age.<sup>6</sup>
3. The dilemma is management of epilepsy in the setting of pregnancy. All AEDs are associated with a risk of major and minor malformation and classified C or D by the FDA. For example Valproic Acid (Depakote) and Carbamazepine (Tegretol) are both associated with increase in neural tube defects. Risks are higher with polytherapy. Standards from at least 2002 were that monotherapy should be used if seizures are well controlled. If seizures are poorly controlled, adequate seizure control is the primary goal. These rules apply to grand mal and generalized tonic clonic seizures. Minor seizures, like petit mal are not as dangerous. Prenatal counseling is important. AED treatment should be optimized prior to pregnancy. Vitamin K should be administered during the last 4 weeks. A large retrospective study, reported in 2001, screening 128,409 pregnancies showed that women taking AED had increased risk of anomalies (including minor) compared with control individuals (20.6% vs 8.5%). The incidence of major malformation was 5.7% for infants exposed to AED versus 1.8% for control individuals. The risk of major malformation increased to 8.6% for infants exposed to two or more AEDs, confirming the higher risk for polytherapy. Women with epilepsy not taking AEDs had no increased risk compared with the control group. However, women treated with AEDs may have had more severe epilepsy than women who were not treated had. Therefore, this does not completely exclude selection bias and contribution of maternal epilepsy to teratogenicity. Holmes LB, Harvey EA, Coull BA, et al.: The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001, 344:1132–1138.
4. Dose dependent risks for Valproic Acid and Carbamazepine is demonstrated in some studies.<sup>7</sup>
5. Topiramate is one of the “newer” AEDs. (others include Neurontin and Lamictal). As of 2002 the teratogenicity of these drugs was uncertain. In animal studies, Lamictal and Neurontin were safe but Topiramate was not, causing limb malformations in rats and rabbits.

<sup>4</sup> Romitti, P.A., Lidral, A.C., Munger, R.G., Daack-Hirsch, S., Burns, T.L., & Murray, J.C. (1999). Candidate gene for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: Evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts. *Teratology*, 59(1), 39-50

<sup>5</sup> Lettieri, J. (1993). Lip and oral cavity. In R.E. Stevenson, J.G. Hall, & R.M. Goodman (Eds.), *Human malformations and related anomalies* (pp. 367-374). New York: Oxford University Press. And Shaw, G.M., Wasserman, C.R., Murray, J.C., & Lammer, E.J. (1998). Infant TGF-alpha genotype, orofacial clefts, and maternal periconceptional multivitamin use. *Cleft Palate—Craniofacial Journal*, 35(4), 366-370.

<sup>6</sup> *Epilepsy in Pregnant Women*, M. Bruno MD, C. Harden MD, 2002

<sup>7</sup> Kaneko S, Battino D, Andermann E, et al.: Congenital malformations due to antiepileptic drugs. *Epilepsy Res* 1999, 33:145–158. 8. Samren EB, van Duijn CM, Koch S, et al.: Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 1997, 38:981–990.



### C. AEDs and Contraceptives

Topamax is among the AEDs that interact with contraceptive hormones. Phenobarbital (phenobarbitone), phenytoin, carbamazepine, oxcarbazepine, felbamate and topiramate all have been shown to increase the metabolism of ethinylestradiol and progestogens and therefore reduce the effectiveness of these contraceptives. Therefore, if a woman is on one of the AEDs and wishes to take the oral contraceptive pill, she needs to take a preparation containing at least 50mg of ethinylestradiol. Levonorgestrel implants are contraindicated in women receiving these AEDs because of cases of contraceptive failure. It is recommended that medroxyprogesterone injections be given every 10 rather than 12 weeks to women who are receiving AEDs that induce hepatic microsomal enzymes. There are no interactions between the combined oral contraceptive pill, progesterone- only pill, medroxyprogesterone injections or levonorgestrel implants and the AEDs valproic acid (sodium valproate), vigabatrin, lamotrigine, gabapentin, tiagabine, levetiracetam, zonisamide, ethosuximide and the benzodiazepines. Notice topiramate is not listed. Therefore, normal dose contraceptive preparations can be used in patients receiving these AEDs .

### D. Reports of increased risk of CL/CP

1. 2002 Topiramate passes freely over the placenta in a one to one ratio. I. Ohman, *Epilepsia*, 43(10):1157–1160, 2002.
2. 2008 S. Hunt, Topiramate in Pregnancy: Preliminary Experience from the UK Epilepsy and Pregnancy Register. Data through August 31, 2007, completed November 19, 2007, accepted April 2, 2008, published July 22, 2008. Major congenital malformation (MCM) rate similar to other AEDs in monotherapy. Pregnancies exposed to topiramate were 178 of which 16 had a MCM (9%, CI 5.6%—14.1%). Four were oral clefts (2.2% CI 0.9%—5.6%). Notably, 2 of the clefts were monotherapy out of only 61 cases (3.3%).

#### DISCUSSION

The MCM rate for monotherapy exposures to topiramate was well within the range quoted for other AEDs. For polytherapy exposures the MCM rate was higher, consistent with previous reports comparing monotherapy and polytherapy exposures to all AEDs. The MCM rates for combinations containing valproate in addition to topiramate were higher than for combinations not containing valproate. While it is not clear if this is a consequence of an interaction between these drugs, is a reflection of unidentified patient characteristics, or is due to valproate, which has increasingly been shown to be associated with a high risk of MCMs, either in monotherapy or as part of a polytherapy regimen, is unclear. Clearly these results need to be replicated in larger numbers and from different registers before we might counsel women of child-bearing age against using combinations including topiramate and valproate. We found the rates of oral clefts (2.2%) and hypospadias (5.1%) much higher than that reported in the United Kingdom. For oral clefts, which occur in 1 in 500 live births in the United Kingdom,<sup>13</sup> the observed rate was 11 times higher than the background rate.

While our results are preliminary, they are relevant not only in dealing with women with epilepsy of childbearing years. Topiramate is also licensed for use for migraine prophylaxis, an even more common condition which also occurs frequently in women of childbearing years. While the risks for adverse outcomes, including teratogenic endpoints, may differ between patient groups exposed to the same drug but used for different indications, the teratogenic potential of any agent is also likely determined by factors related to the structure and functional effects of the agent, the dose prescribed, and the timing of use. This is also likely to be the case for topiramate. Monitoring pregnancies in women with migraine exposed to topiramate should therefore be encouraged



3. 2009 Hernandez-Diaz S., Presentation W9 Teratology Society Program p.408 (2009). The North American AED Pregnancy Registry has enrolled 6,456 women since 1997 and 372 friends and family members not taking AED. This study compared frequency of adverse pregnancy outcomes in topiramate users in monotherapy and controls. Major Malformations when exposed in 1<sup>st</sup> trimester 3.8%, compared to 1.3% unexposed, RR 2.8 (95% CI 1.0-8.1). The corresponding RR's for lamotrigine (Lamictal) and carbamazepine (Tegretol) were 1.3 and 2.1 (not statistically significant). Four infants exposed to topiramate had cleft lip/palate. (11 total malformation in 289 subject).
4. 2011 FDA Drug Safety Communication on risk of oral clefts in children born to mothers taking Topamax (topiramate). From the North American Antiepileptic Drug Pregnancy Registry (NAAED), compared to other AEDs, the RR was 2.55—3.68. The RR compared to infants of mothers without treatment with other AEDs was 21.3 (CI 7.9—57.1).

Data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.4% compared to a prevalence of 0.38%—0.55% in infants exposed to other antiepileptic drugs (AEDs), and a prevalence of 0.07 % in infants of mothers without epilepsy or treatment with other AEDs. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 21.3 as compared to the risk in a background population of untreated women (95% Confidence Interval:7.9—57.1). The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts (3.2 %) among infants exposed to topiramate monotherapy, a 16-fold increase in risk compared to the risk in their background population (0.2%).

## E. Registries

There are several pregnancy registries monitoring the outcomes of antiepileptic drug (AED) exposed pregnancies worldwide: the North American Pregnancy Registry, the United Kingdom Epilepsy and Pregnancy Register, the Australian Registry of Antiepileptic Drugs in Pregnancy, the International Lamotrigine Registry, and the European Pregnancy Registry.

## F. What they knew and when they knew it

1. Pre Approval—Abnormalities in the babies of pregnant mice, rats and rabbits. See p.2 above
2. 1998. A case report, multiple minor anomalies were described in an infant born to a mother treated with topiramate 700mg twice daily as monotherapy throughout gestation. At birth, the child was noted to have prenatal-onset growth deficiency, generalized hirsutism, a third fontanelle, a short nose with anteverted nares, blunt distal phalanges and generalized blunting of the nails, with fifth nail hypoplasia. Some of these features are found in children exposed to different AEDs in utero. The authors concluded that genetic factors might be involved. Hoyme HE. Hauck L. Quinn D. Minor anomalies accompanying prenatal exposure to topiramate [abstract]. *Epilepsia* 1998; 56 (1): 119A
3. 1999 Topiramate produced right sided congenital absence of all or part of a digit (ectrodactyly) in rats and rib and vertebral malformations in rabbits. Glauser TA. Topiramate. *Epilepsia* 1999; 40 Suppl. 5: S71-80.



### TOPOMAX AND BIRTH DEFECTS

Copyright © 2004–2011 All rights reserved. Anapol Schwartz.  
Read more information online at [www.anapolschwartz.com](http://www.anapolschwartz.com).



4. 2002 Palmieri C, Canger R. Teratogenic potential of the newer antiepileptic drugs and how should this influence prescribing. *CNS Drugs* 2002;16:755–64. In mice even doses that are 20% of the human dose produced malformations, mainly of the craniofacial complex. In rats, doses as low as 20% of the human dose, reduced fetal bodyweight and higher doses produced various craniofacial and limb anomalies. In rabbits, an increase in intrauterine fetal death occurred at twice the human dose; only higher doses produced skeletal abnormalities, but at these doses evidence of maternal toxicity was observed.

Teratogenic potential of the newer antiepileptic drugs: what is known and how should this influence prescribing? Palmieri C, Canger R. Regional Epilepsy Center, University of Milan Medical School, San Paolo Hospital, Milan, Italy.

ABSTRACT

The treatment of women of childbearing age who have epilepsy raises many questions because of the interactions between epilepsy, anti-epileptic therapy and different aspects of reproductive life. Menstrual cycle disorders and reduced fertility have been partially ascribed to antiepileptic drugs (AEDs). Furthermore, most AEDs induce the cytochrome P450 (CYP) enzymatic system, altering the metabolism of sex hormones and contributing to the failure of oral contraceptives. Pregnancy represents, in this context, the most critical period because of the well known teratogenic potential of all established AEDs. For most of these drugs no specific patterns of malformations have been identified, although during the past few decades basic knowledge has been acquired, particularly concerning the mechanisms of AED-induced teratogenesis and related risk factors. These issues form the basis of the current guidelines for the management of epilepsy in pregnant women. In the past decade, several new AEDs have been introduced into clinical practice. For a number of reasons, these drugs appear to be more favourable than the older ones as treatments for epilepsy in women of childbearing age. They possess a good pharmacokinetic profile that makes them more stable during pregnancy, and they have a low potential for interaction with other drugs. They are also less likely than the older AEDs to be metabolised to compounds that are teratogenic. Furthermore, most of them do not possess antifolate properties. With the exception of topiramate and vigabatrin, the newer AEDs do not appear to be teratogenic in animals when administered in subtoxic doses. However, animal teratology may not be a reliable predictor of human teratogenicity, and there is a significant lack of information regarding the teratogenic profile of these newer agents in humans. Because clinical experience with these agents is limited, it is advisable to avoid exposure of the embryo to these drugs when pregnancy is planned. The establishment of pregnancy registries could allow for the rapid collection of data related to the administration of new AEDs in pregnancy and the outcomes of such exposure.

5. 2005—A case report of a child whose mother received Topamax throughout pregnancy born with bone abnormalities in his thumbs and toes and a muscle abnormality in the mouth. Vila Ceren, C; et al Topiramate and Pregnancy: Neonate with Bone Abnormalities: *Annals Pediatrics (Barc)* 2005;63:363-5.



6. 2006 Kwarta RF, Hulihan JF, Schmider J, Nye JS. Pregnancy outcomes in topiramate-treated women. *Epilepsia* 2006; 47, suppl 4:119–204. Abstract. A company sponsored abstract reporting outcomes for 75 pregnancies exposed to Topamax. Of 29 monotherapy exposures there were two malformations. Micrognathia (abnormally small lower jaw.) and Phimosis (inability to retract the distal foreskin over the glans penis). Of the remaining 46 pregnancies where topiramate was used along with at least 1 other AED, 7 babies had malformations including a cleft palate, cleft lip and cleft lip/cleft palate.

TOPOMAX AND BIRTH DEFECTS

Copyright © 2004–2011 All rights reserved. Anapol Schwartz.  
Read more information online at [www.anapolschwartz.com](http://www.anapolschwartz.com).



7. 2006 J. Morrow, Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. , J.Neurology Neurosurgery Psychiatry, 2006:77; 193-198. Only 35 pregnancies exposed to Topiramate.

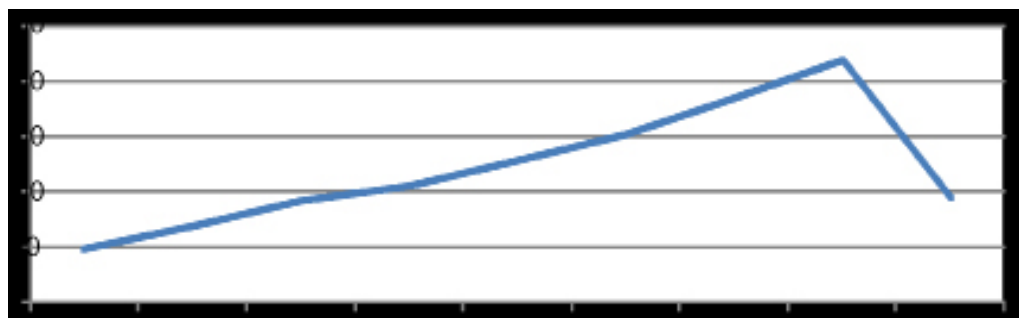
Clearly there is a need for further data to be collected to estimate the risks of all available AEDs in pregnancy, and not only for MCMs. Notwithstanding some methodological concerns, pregnancy registers seem the only feasible way of collecting the data required to signal such safety concerns for particular AEDs or regimes. The UK Epilepsy and Pregnancy Register continues to collect information and welcomes new referrals. Our study supports the idea that there are differences between AEDs and highlights areas of concern. That almost 96% of infants born to women with epilepsy did not have an MCM, however, is a message that is likely to be reassuring both to women with epilepsy and to those who care for them.

8. 2007 A. Ornoy, Reproductive Toxicology 25(2008)388-389. A study of 52 pregnancies with 41 live births, 29 on monotherapy and 23 on polytherapy between January 1996 and December 2006. . No increased risk of major malformation.
9. 2008 Topiramate induced histopathological changes in the placenta of rats. A. Mishra, Indina Journal of Experimental Biology, vol. 46, pp.715-719 October 2008. "The results suggest that topiramate induced dose dependent deleterious changes in the structure of placenta, therefore it should be used with caution in pregnancy.

#### G. The Corporations

1. Ortho-McNeil Pharmaceuticals Inc. is a New Jersey Corporation with a principle place of business in Rareitan, NJ.
2. Ortho-McNeill Neurologics, Inc. is a division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. and is a New Jersey corporation, with a principle place of business in Titusville, NJ.
3. Ortho-McNeil-Janssen Pharmaceuticals Inc. is a Pennsylvania Corporation with a principle place of business in Titusville, NJ.
4. Johnson & Johnson International is a New Jersey corporation with principle place of business in New Brunswick, NJ.
5. Beginning in 2009, 19 generic manufacturers were licensed to sell topiramate. They are listed on attachment A. Nine of these companies are either headquartered in or incorporated in Pennsylvanian or New Jersey.
6. Sales for Topamax

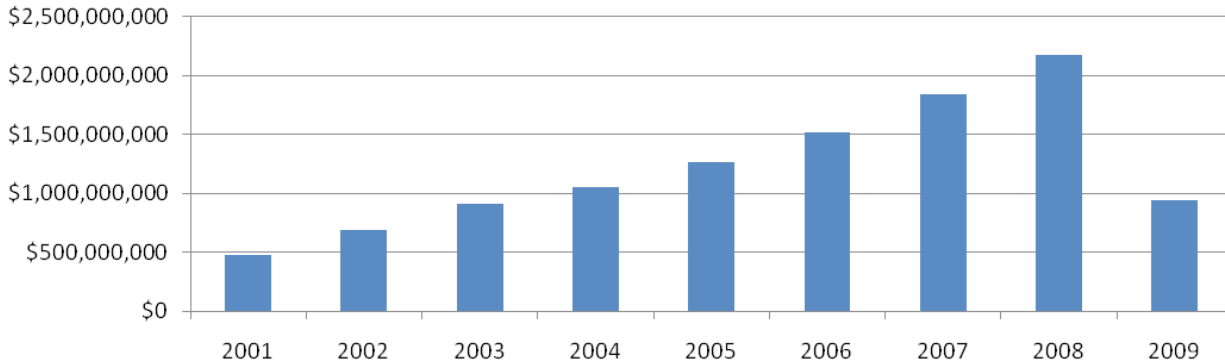
2009—\$939,312,000 (rank 37)  
 2008—\$2,177,000,000 (rank 13)  
 2007—\$1,837,000,000 (rank 13)  
 2006—\$1,520,000,000 (rank 20)  
 2005—\$1,267,766,000 (rank 25)  
 2004—\$1,052,000,000 (rank 32)  
 2003—\$912,933,000 (rank 35)  
 2002—\$687,000,000 (rank 94)  
 2001—\$477,000,000



#### TOPOMAX AND BIRTH DEFECTS



## Sales



7. From January 2007 through December 2010 approximately 32.3 million topiramate prescriptions were dispensed and approximately 4.3 million Patients filled prescriptions from outpatient retail pharmacies in the United States.<sup>8</sup>

## H. Topamax—Approved December 24, 1996— NDA 020505

### 1. Indication

- a. Initial approval 12/24/96—“as adjunctive therapy for adults with partial onset seizures.”
- b. 7/26/1999—added pediatric patients—“as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures. ”
- c. 10/5/1999—Add generalized tonic-clonic seizures: —“as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures, or primary generalized tonic-clonic seizures. ”
- i. Generalized Tonic-Clonic seizures—A seizure is an abnormal paroxysmal discharge of cerebral neurons due to cortical hyperexcitability. The International Classification of Seizures divides seizures into 2 categories: partial seizures (ie, focal or localization-related seizures) and generalized seizures.

Partial seizures result from a seizure discharge within a particular brain region or focus, and they manifest focal symptoms. Generalized seizures probably begin in the thalamus and other subcortical structures, but on scalp EEG recordings they may appear to start simultaneously in both cerebral hemispheres; therefore, they manifest symptoms bilaterally in the body and are always associated with loss of consciousness.

Partial seizures can generalize secondarily and result in tonic-clonic activity. Some partial seizures have very rapid generalization, and the partial phase of the seizure may not be readily apparent clinically or even on scalp EEG recordings. However, secondarily generalized partial seizures are not included in the category of generalized seizures, which includes only primary generalized seizures.

<sup>8</sup> SDI, Vector One®: National (VONA) and Total Patient Tracker (TPT). January 2007-December 2010. Data extracted 2-9-11 as reported in the FDA Drug Safety Communication 03-04-2011 <http://www.fda.gov/Drugs/DrugSafety/ucm245085.htm>

Generalized convulsive seizures can be classified as atonic, tonic, clonic, tonic-clonic, myoclonic, or absence on the basis of clinical symptoms and EEG abnormalities. Tonic seizure is the rigid contracture of muscles, including respiratory muscles, which is usually brief. The clonic component is the rhythmic shaking that occurs and is longer. Together, a generalized tonic-clonic seizure (GTCS) is also called a grand mal seizure and is one of the most dramatic of all medical conditions.

Several epilepsy syndromes have generalized seizures: [benign neonatal convulsions](#), [benign myoclonic epilepsy of infancy](#), childhood absence epilepsy, juvenile absence epilepsy, [juvenile myoclonic epilepsy](#), and generalized tonic-clonic seizures upon awakening.

## In general, there are 2 kinds of partial seizures: simple and complex.

In a Simple Partial Seizure, a person:

- Stays alert
- Can answer questions and follow commands
- Can recall what happened during the seizure

In a Complex Partial Seizure, a person:

- Loses or has a change in consciousness
- May not be able to answer questions or follow commands
- Often cannot recall what happened during part or all of the seizure



- d. 8/28/2001—Added “in patients 2 years of age or older with seizure associated with Lennox-Gastaut syndrome.” Lennox-Gastaut Syndrome is Childhood epileptic encephalopathy (Lennox-Gastaut syndrome [LGS]) is a devastating pediatric epilepsy syndrome constituting 1-4% of childhood epilepsies. The syndrome is characterized by multiple types of seizures, mental retardation or regression, and abnormal EEG with generalized slow spike-and-wave discharges (1.5-2 Hz). The most common seizure types are tonic-axial, atonic, and absence seizures, but myoclonic, generalized tonic-clonic, and partial seizures can be observed. Seizures often are resistant to therapy.



- e. 8/10/2004—Migraine Headache Prophylaxis in adults—in a 2001 report to the journal “Headache” it was estimated that in 1999 almost 28 million Americans suffered from migraine headaches. B Lipton et al Headache, 2001;41:646-657

Note the following: Neurology 2007;68;343-349

Migraine prevalence, disease burden, and the need for preventive therapy

R. B. Lipton, MD, [M. E. Bigal](#), MD, PhD,  
[M. Diamond](#), MD, [F. Freitag](#), DO,  
[M. L. Reed](#), PhD, [W. F. Stewart](#), PhD and

on behalf of the AMPP Advisory Group\*

± Author Affiliations

From the Department of Neurology (R.B.L., M.E.B.) and Department of Epidemiology and Population Health (R.B.L.), Albert Einstein College of Medicine, Bronx, NY; The Montefiore Headache Center, Bronx, NY (R.B.L., M.E.B.); The New England Center for Headache, Stamford, CT (M.E.B.); Diamond Headache Center, Chicago, IL (M.D., F.F.); Vedanta Research, Chapel Hill, NC (M.L.R.); and Center for Health Research & Rural Advocacy, Geisinger Clinic, Danville, PA (W.F.S.).

ABSTRACT

Objectives: 1) To reassess the prevalence of migraine in the United States; 2) to assess patterns of migraine treatment in the population; and 3) to contrast current patterns of preventive treatment use with recommendations for use from an expert headache panel.

Methods: A validated self-administered headache questionnaire was mailed to 120,000 US households, representative of the US population. Migraineurs were identified according to the criteria of the second edition of the International Classification of Headache Disorders. Guidelines for preventive medication use were developed by a panel of headache experts. Criteria for consider or offer prevention were based on headache frequency and impairment.

Results: We assessed 162,576 individuals aged 12 years or older. The 1-year period prevalence for migraine was 11.7% (17.1% in women and 5.6% in men). Prevalence peaked in middle life and was lower in adolescents and those older than age 60 years. Of all migraineurs, 31.3% had an attack frequency of three or more per month, and 53.7% reported severe impairment or the need for bed rest. In total, 25.7% met criteria for “offer prevention,” and in an additional 13.1%, prevention should be considered. Just 13.0% reported current use of daily preventive migraine medication.

Conclusions: Compared with previous studies, the epidemiologic profile of migraine has remained stable in the United States during the past 15 years. More than one in four migraineurs are candidates for preventive therapy, and a substantial proportion of those who might benefit from prevention do not receive it.

\*The AMPP Advisory Group: Richard B. Lipton, MD (principal investigator); Marcelo E. Bigal, MD, PhD; Dawn Buse, MD; Michael L. Reed, PhD; Walter Stewart, PhD; Merle Diamond, MD; Frederick Freitag, DO; Elisabeth Hazard, PhD; Jonothan Tierce, CPhil; Elizabeth Loder, MD; Paul Winner, MD; Stephen Silberstein, MD; Suzanne Simons; and Seymour Diamond, MD.

Disclosure: This study was sponsored by the National Headache Foundation through a grant from Ortho-McNeil Neurologics, Inc. Drs. Lipton, Bigal, Reed, Freitag, and Diamond have received grants and honoraria in excess of \$10,000 from Ortho-McNeil Neurologics Inc. Dr. Stewart has nothing to disclose.

- f. 6/29/2005—Monotherapy in Epilepsy—“indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures.”



2. Off Label Uses—

- a. As reported by Consumer Reports: Bipolar disorder, depression, nerve pain.
- b. As alleged in a False Claims Act case filed in the district of Massachusetts 1:03-cv-11445-WGY:

- 01. Pediatric Bipolar Disorder
- 02. Juvenile Myoclonic Epilepsy (“JME”)
- 03. Binge Eating
- 04. Tourette’s Syndrome
- 05. Bullimia Nervosa
- 06. Infantile Spasms
- 07. Headache Pain in Pediatric Patients
- 08. Obesity
- 09. Anxiety Disorders (Post Traumatic Stress Disorder (“PTSD”).
- 10. Disorders of Aggression
- 11. Bipolar Disorder
- 12. Mood Stabilization
- 13. Absence Seizures
- 14. Essential Tremor
- 15. Neuropathic Pain
- 16. Neuroprotection
- 17. Sleep Apnea
- 18. Parkinson’s Disease
- 19. Stroke
- 20. ALS
- 21. Pseudotumor Cerebri
- 22. Monotherapy
- 23. Nicotine Addiction
- 24. Alcoholism
- 25. Diabetes
- 26. Drug Addiction

c. As alleged in the False Claims Act complaint 1:03-cv-11445-WGY, in 2002, 60% of Topamax sales were off –label.



TOPOMAX AND BIRTH DEFECTS

Copyright © 2004–2011 All rights reserved. Anapol Schwartz.  
Read more information online at [www.anapolschwartz.com](http://www.anapolschwartz.com).



## I. Warnings re Pregnancy.

### Until March 4, 2011 Pregnancy Category C.

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD=400 mg/day) on a mg/m<sup>2</sup> basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain. In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30 and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m<sup>2</sup> basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m<sup>2</sup> basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m<sup>2</sup> basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m<sup>2</sup> basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above. When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m<sup>2</sup> basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m<sup>2</sup> basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater. In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30 or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m<sup>2</sup> basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m<sup>2</sup> basis) and higher.

There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. In post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.

### On March 4, 2011 changed to Pregnancy D and WARNING added

#### Warning: 5.6 Fetal Toxicity

TOPAMAX® can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring [see Use in Special Populations (8.1)].

Consider the benefits and the risks of TOPAMAX® when administering this drug in women of childbearing potential, particularly when TOPAMAX® is considered for a condition not usually associated with permanent injury or death [see Use in Special Populations (8.9) and Patient Counseling Information (17.8)]. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Special Populations (8.1) and (8.9)].



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category D. [see Warnings and Precautions (5.6)] TOPAMAX® can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Special Populations (8.9)].

#### Pregnancy Registry

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1888-233-2334. Information about the North American Drug Pregnancy Registry can be found at <http://www.massgeneral.org/aed/>.

#### Human Data

Data from the NAAED Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.4% compared to a prevalence of 0.38%—0.55% in infants exposed to other AEDs, and a prevalence of 0.07% in infants of mothers without epilepsy or treatment with other AEDs. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a background rate of 0.17%. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 21.3 (95% Confidence Interval=CI 7.9—57.1) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%.

Topiramate treatment can cause metabolic acidosis [see Warnings and Precautions (5.4)]. The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) can cause decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor. Pregnant patients should be monitored for metabolic acidosis and treated as in the nonpregnant state [see Warnings and Precautions (5.4)]. Newborns of mothers treated with topiramate should be monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth.

#### Animal Data

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in multiple animal species at clinically relevant doses. When oral doses of 20, 100 or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD) 400 mg/day on a mg/m basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

#### TOPOMAX AND BIRTH DEFECTS

Copyright © 2004–2011 All rights reserved. Anapol Schwartz.  
Read more information online at [www.anapolschwartz.com](http://www.anapolschwartz.com).



In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m basis) and reductions in pre-and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30 or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m basis) and higher.

## J. Corporate Malfeasance related to Topamax

### Guilty plea

## ORTHO-McNEIL PHARMACEUTICAL, LLC PLEADS GUILTY TO ILLEGAL PROMOTION OF TOPOMAX AND IS SENTENCED TO CRIMINAL FINE OF \$6.14 MILLION

BOSTON, Mass. - ORTHO-McNEIL PHARMACEUTICAL, LLC, a subsidiary of Johnson & Johnson, pled guilty today in U.S. District Court in Boston to one count of misdemeanor violation of the Food, Drug & Cosmetic Act for illegally promoting its epilepsy drug Topamax for uses that were not approved by the FDA. The company was also sentenced at today's hearing.

United States Attorney Carmen M. Ortiz and Tony West, Assistant Attorney General for the Civil Division of the Department of Justice announced today that ORTHO-McNEIL PHARMACEUTICAL, LLC was sentenced by U.S. Magistrate-Judge Robert B. Collings to pay a criminal fine of \$6.14 million. Hess was charged in September 2009 and later pleaded guilty.

At the plea hearing, the prosecutor told the Court that had the case proceeded to trial, the Government's evidence would have proven that ORTHO-McNEIL PHARMACEUTICAL, LLC had a promotional program called the "Doctor for a Day Program" as a tool to promote its epilepsy drug, Topamax, for uses which had never been approved by the United States Food & Drug Administration (FDA). Through the "Doctor for a Day Program," ORTHO-McNEIL PHARMACEUTICAL, LLC paid outside physicians to accompany sales representatives on sales calls, including to psychiatrists. On these sales calls, through the Doctor for a Day, ORTHO-McNEIL PHARMACEUTICAL, LLC promoted Topamax to psychiatrists, including some in Massachusetts, for psychiatric uses. However, ORTHO-McNEIL PHARMACEUTICAL, LLC had never applied to the FDA for any approval for Topamax to treat any psychiatric disorders and there was no data from any well-controlled clinical trial to demonstrate that Topamax was safe and effective to treat any psychiatric conditions.

"This case should send a strong reminder that the off-label promotion of pharmaceuticals is illegal, whether it is done directly by company employees, or through programs such as the 'Doctor For A Day Program,' said United States Attorney Carmen M. Ortiz. "We will remain vigilant in our enforcement of these laws regardless of what form the conduct takes," Ortiz concluded.

An affiliate of ORTHO-McNEIL PHARMACEUTICAL, LLC called Ortho-McNeil-Janssen Pharmaceuticals, Inc. will also pay \$75.37 million to resolve civil allegations under the False Claims Act that it illegally promoted Topamax and caused false claims to be submitted to government health care programs for a variety of psychiatric uses that were not medically accepted indications and therefore not covered by those programs. Also as part of the settlement, Ortho-McNeil-Janssen Pharmaceuticals entered into a corporate integrity agreement with the Office of Inspector General of the Department of Health and Human Services.



The criminal case was prosecuted by Assistant U.S. Attorneys Jeremy Sternberg and Susan Winkler of the U.S. Attorney’s Office for the District of Massachusetts and Jill Furman of the Justice Department’s Office of Consumer Litigation. It was investigated by the U.S. Department of Veterans Affairs, Office of Inspector General, Boston Resident Agency, Criminal Investigations Division, the U.S. FDA’s Office of Criminal Investigations, Boston Resident Office and the Federal Bureau of Investigation’s Boston Field Office.

The civil investigation and settlement was handled by Assistant U.S. Attorney Zachary A. Cunha of the U.S. Attorney’s Office in Massachusetts and Trial Attorney Colin M. Huntley of the Commercial Litigation Branch of the Justice Department’s Civil Division. The Corporate Integrity Agreement was negotiated by the Office of Inspector General for the Department of Health and Human Services. Assistance was provided by the National Association of Medicaid Fraud Control Units and the offices of various state Attorneys General.

## K. Case Acceptance Criteria

1. Mother ingested Topamax (or topiramate) after conception and during the first trimester. Careful review is necessary as the actual date of conception can never be precisely determined.
2. Child is born with cleft lip, cleft palate or both.
3. Find out what other medications, if any, mother was taking during pregnancy
4. Find out if family has any history of cleft lip or cleft palate.
5. Find out about other potentially toxic exposures including but not limited to maternal alcohol use, maternal cigarette smoking, other antiepileptic drugs (phenytoin, valproic acid), thalidomide, dioxin (pesticide), and retinoic acid. Also find out if there is any evidence of maternal malnutrition.
6. Numbers 1 and 2 are mandatory. Numbers 3-5 are considerations.

### EXHIBIT B-1

## TOPAMAX APPROVAL HISTORY NDA 020505

Action Date	Supplement Number	Approval Type
12/24/1996	000	Approval
07/23/1999	001	New or Modified Indication
10/01/1999	003	New or Modified Indication
08/28/2001	002	New or Modified Indication
08/11/2004	022	New or Modified Indication
06/29/2005	018	New or Modified Indication



EXHIBIT B-2—07/23/1999 Indications

INDICATIONS AND USAGE: TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2—16 years with partial onset seizures, or primary generalized tonic-clonic seizures.

EXHIBIT B-3—10/1/1999 Indications

INDICATIONS AND USAGE: TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2—16 years with partial onset seizures, or primary generalized tonic-clonic seizures.

EXHIBIT B-4—8/28/2001 Indications

INDICATIONS AND USAGE: TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2—16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

EXHIBIT B-5—8/11/2004 Indications

INDICATIONS AND USAGE: Epilepsy  
TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2—16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

EXHIBIT B-6—6/29/2005 Indications

INDICATIONS AND USAGE

**Monotherapy Epilepsy**

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures.

Effectiveness was demonstrated in a controlled trial in patients with epilepsy who had no more than 2 seizures in the 3 months prior to enrollment. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials.

**Adjunctive Therapy Epilepsy**

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

**Migraine**

TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated for adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX® in the acute treatment of migraine headache has not been studied.

TOPOMAX AND BIRTH DEFECTS

Copyright © 2004–2011 All rights reserved. Anapol Schwartz.  
Read more information online at [www.anapolschwartz.com](http://www.anapolschwartz.com).

