



*This information has been gathered by The Cleft Lip & Palate Foundation of Smiles. We are responding to the fact that a number of our members have questions concerning the safety of medications that they had taken during pregnancy, or may take during a future pregnancy. These medications may be the cause of craniofacial differences. Our goal is to ensure that our families have resources and facts about the medications that may be taken during pregnancy, so you can have informed discussions with the treating doctors.*

Online at [www.cleftsmile.org](http://www.cleftsmile.org)

Contact us by email at [rachel@cleftsmile.org](mailto:rachel@cleftsmile.org)

The Cleft Lip & Palate Foundation of Smiles provides research on craniofacial causes (genetics, environmental, prescription drugs), treatments (cleft palate teams, medical devices, therapies), and available support for families.

*This PDF is about Topamax birth defect risks for women who get pregnant. The use of Topamax for childbearing-age women who are trying to prevent migraine headaches or manage epilepsy seizures raises difficult questions as to the importance of evaluating the risks vs. the benefits.*

*Topamax and topiramate are used interchangeably.*



## RESEARCH AND RECENT STUDIES

# Causes of Cleft Lip and Palate: TOPAMAX

### What is Topamax?

Topamax or its generic equivalent topiramate is an anti-seizure medication also used to prevent migraine headaches. Topamax has also been used off-label to treat mood instability, eating disorders, Parkinson's, stroke, and psychiatric disorders. Anti-epileptic drugs (AEDs) pose concerns about possible teratogenicity. The definition for teratogenicity is an agent, such as a virus, a drug, or radiation that causes malformation of an embryo or fetus.

On March 4, 2011, the FDA released a new MedAlert safety update changing Topamax from a Pregnancy C Category to a Pregnancy D Category and added a warning about pregnancy.

To identify which drugs may have additional risks for babies born to pregnant women, the FDA assigns all approved drugs to Pregnancy Categories based on data obtained through animal studies and clinical studies or experience. It is unethical to perform clinical studies on pregnant women. Pregnancy Categories also help patients and healthcare professionals weigh the risks and benefits of using a drug during pregnancy.

Drugs in Pregnancy Category D have human data demonstrating evidence of human fetal risk, but the potential benefits of these drugs may still be considered acceptable in certain situations.

Topiramate was previously classified as a Pregnancy Category C drug, which means that data from animal studies suggested potential fetal risks, but no adequate data from human clinical trials or studies were available at the time of approval. Topiramate labels are being updated with the new information describing the increased risk of oral clefts.

### How many people took Topamax?

According to the TopamaxEpilepsy.com website, "more than 4 million people worldwide."

Another source, National (VONA) and Total Patient Tracker reports 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.



### Who makes Topamax?

The drug is manufactured by Ortho McNeil.

As a member of the Johnson & Johnson family of companies, Ortho-McNeil Pharmaceuticals Inc. is a New Jersey Corporation with a principal place of business in Raritan, NJ.

Ortho-McNeil Neurologics, Inc. is a division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. and is a New Jersey corporation, with a principal place of business in Titusville, NJ.

Ortho-McNeil-Janssen Pharmaceuticals Inc. is a Pennsylvania Corporation with a principal place of business in Titusville, NJ.

Johnson & Johnson International is a New Jersey corporation with principal place of business in New Brunswick, NJ.

### What is Topiramate?

Topiramate is the generic version Topamax. In April 2009, the FDA approved generic versions of the [anti-seizure drug topiramate](#). Labeling information for generic topiramate will differ from that on Topamax, the branded drug, because some uses of the latter continue to be protected by patents and exclusivity.

The approval covers topiramate tablets in several different strengths from 17 different generic manufacturers. The FDA noted that both generic and branded topiramate come with an important safety warning about metabolic acidosis. This condition, associated with excessive acid in the blood, can cause symptoms such as tiredness, loss of appetite, irregular heartbeat, and impaired consciousness.

Topiramate (and Topamax) have also been associated with serious eye problems, such as a sudden decrease in vision and a blockage of fluid in the eye, causing increased pressure.

Beginning in 2009, 17 generic manufacturers were licensed to sell topiramate.

### Why take Topamax? What is Topamax prescribed for?

Seizures—Why do doctors find it necessary to prescribe Topamax?

This would be a good question for your doctor. Topamax marketing literature touts itself as having a proven safe profile that doesn't cause weight gain, works well with other AEDs, and millions of people have taken the drug.

According to the fine print on the [Topamax-epilepsy.com](#) website, "If you take TOPAMAX® during pregnancy, your baby has a higher risk for birth defects called cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant. There may be other medicines to treat your condition that have a lower chance of birth defects. All women of childbearing age should talk to their healthcare providers about using other possible treatments instead of TOPAMAX®. If the decision is made to use TOPAMAX®, you should use effective birth control (contraception) unless you are planning to become pregnant."

Topiramate is one of the "newer" AEDs; others include Neurontin and Lamictal. As of 2002 the tetratenicity of these drugs was uncertain. In animal studies, Lamictal and Neurontin were safe but topiramate was not, causing limb malformations in rats and rabbits.

As for seizure medication in general, new research on the links between seizure medication and pregnancy complications highlights the hard choices that pregnant women with epilepsy must make.

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Scientists from the University of Bergen in Norway found that women with epilepsy are more likely to have pregnancy complications, and that the added risks were largely “associated with the use of anti-epileptic drugs in pregnancy.”

Women who suffer from epilepsy face especially difficult decisions about how to treat their condition while pregnant.

### What are alternative drugs and treatments? Are there safer drugs?

It’s important that you find a neurologist and an OB/GYN who are familiar with both pregnancy issues and epilepsy, and who can help you figure out the best direction for you. In the meantime, you should be taking a folic acid supplement. Taking folic acid is important for all pregnant women, but exceptionally important for women on anti-epileptic drugs.

### Migraines—Why do doctors prescribe Topamax?

Migraines are a common but complex disorder. Women of childbearing years should not be exposed to harmful drugs that may harm their fetus.

Some people take drugs when a migraine starts but Topamax is taken daily to prevent migraine headaches. While migraines can’t be completely eliminated, Topamax can help stop the headaches before they start, so you can get fewer of them.

According to the [Topamax.com](http://Topamax.com), “If you take TOPAMAX during pregnancy, your baby has a higher risk for birth defects called cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant. There may be other medicines to treat your condition that have a lower chance of birth defects. All women of childbearing age should talk to their healthcare providers about using other possible treatments instead of TOPAMAX.”

### What are alternative drugs and treatments?

Talk to your doctor about alternative drugs and treatments for migraines. While a doctor may say that the risk is low or not worth being concerned about, to a mother of a baby with cleft palate and/or cleft lip, repercussions can be overwhelming. As a migraine sufferer and woman of childbearing age, you have the right to be proactive and ask about safer alternatives. If your doctor has not broached the subject; take the lead.



### Short summary of studies about topiramate risks for pregnant women

From the UK Epilepsy and Pregnancy Register, published 2008: The major congenital malformation (MCM) rate is similar to other AEDs when used as the only drug (monotherapy). Pregnancies exposed to topiramate were 178 of which 16 or 9% had a MCM; four were oral clefts. Notably, two of the clefts were monotherapy from only 61 cases or 3.3% risk factor.

The [North American Antiepileptic Drug \(NAAED\) Pregnancy Registry](#) has enrolled 6,456 women since 1997 plus 372 friends and family members not taking AEDs. This study compared frequency of adverse pregnancy outcomes in topiramate users in monotherapy and controls. 3.8 % of major congenital malformations when exposed in the first trimester compared to 1.3% unexposed. The corresponding relative risks for lamotrigine (Lamictal) and carbamazepine (Tegretol) were 1.3 and 2.1, not statistically significant. Four infants exposed to topiramate had cleft lip/palate. (Published 2009)





Data from the North American Antiepileptic Drug 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 and a prevalence of 0.07 % in infants of mothers without epilepsy or treatment with other AEDs. (Published 2011)

### **Do you have more questions? Do you need resources?**

For questions and resources about cleft lip and cleft palate, please contact: [The Cleft Lip and Palate Foundation of Smiles](#). Cleft lip or palate is

one of the most common birth defects, currently affecting one in 600 children in the United States. The Foundation was formed by a young mother of twins both born with cleft lip and palate. The Foundation offers positive support to parents of children with craniofacial differences by offering news, information on cleft palate teams, [state by state resources](#), [birth registry listings](#), and a [support group](#) where you can meet other families in your local area who are going through the same or similar concerns and where you can share and express useful information.

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## **References**

FDA announces birth defect risks in women who took topiramate during pregnancy; March 4, 2011.

Questions and Answers: Risk of oral clefts (cleft lip and/or palate) in infants born to mothers taking Topamax (Topiramate)

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Generic Topiramate Wins FDA Approval, Medpage Today, April 2, 2009

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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.

2009 Hernandez-Diaz S., Presentation W9 Teratology Society Program p.408 (2009)

2011 FDA Drug Safety Communication on risk of oral clefts in children born to mothers taking Topamax (topiramate).

## **Other Research from The Cleft Lip & Palate Foundation of Smiles**

Research and Recent Studies:

[Causes of Cleft Lip and Palate: Birth Defects](#)

[Causes of Cleft Lip and Palate: Clomid](#)

[Causes of Cleft Lip and Palate: Health Insurance](#)

[Causes of Cleft Lip and Palate: Hydrocodone](#)

[Causes of Cleft Lip and Palate: Special Education](#)

[Causes of Cleft Lip and Palate: SSRIs](#)