SAFETY REVIEW: TOPIRAMATE USE DURING PREGNANCY

<table>
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<tr>
<th>Application Type</th>
<th>NDA</th>
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<td>Application Number(s)</td>
<td>020-505, 020-844</td>
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<td>Priority or Standard</td>
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Submit Date(s)       June 1, 2010  
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Division / Office     Division of Neurology Products  
                      Office of New Drugs (OND)

Reviewer Name(s)      M. Lisa Jones, MD MPH  
Review Completion Date March 3, 2010

Established Name      Topiramate  
(Proposed) Trade Name Topamax ®  
Therapeutic Class     Anti-epileptic Drug (AED)  
Applicant             Johnson and Johnson Pharmaceutical Research and Development, LLC

Formulation(s)       Oral  
Dosing Regimen       Variable  
Indication(s)         Epilepsy, Migraine Prophylaxis  
Intended Population(s) Patients with epilepsy; Patients with migraines
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1. INTRODUCTION

1.1 Documents Used in this Review

1.1.1 Sponsor Documents


1.1.2 Other Documents

1.1.3 FDA Documents

1. NDA 022-580: Phentermine and Topiramate (Qnexa ®). Consult “for adverse pregnancy outcomes in AERS database such as congenital anomalies associated with the use of topiramate and phentermine separately and co-administered”. Prepared by Dr. Sonia Tabacova. Dated March 10, 2010.

1.2 Review Content

This review examines documents related to the issue of congenital malformations following prenatal exposure to topiramate. These documents include:

1. Annual reports on topiramate from the North American Anti-Epileptic Drug (NAAED) pregnancy registry for 2009 and 2010
2. Consult describing the FDA AERS Case Series
3. Consult from the FDA Maternal Health Team
4. Review of 34 pregnancies occurring during the Qnexa ® (phenteramine/topiramate combination drug) development program
5. Publications from the medical literature

The review concludes that due to biologic plausibility, the strength of the signal and the replication of the signal across data sources that prenatal topiramate contributes to an elevated risk of oral clefts. For the same reasons, the review also concludes that exposure to topiramate during pregnancy is causally associated with decreased fetal weight at birth. The sponsor submitted Changes Being Effected (CBE) labeling supplements updating the pregnancy information for both issues: oral clefts and decreased birth weight. Proposed
labeling based on the sponsor’s proposal and reviewer recommendations for the low birth weight label is presented in Section 3 of this review.

The current topiramate pregnancy labeling describes the preclinical findings and states that human data is not available. These circumstances are consistent with Pregnancy Category C (see Attachment 9.3 for details) and topiramate is currently categorized as such. However, given the human data which is now available and described in this review, the issue of pregnancy category should re-visited. As per the category descriptions, this review concludes that Pregnancy Category D is more appropriate.

1.3 Topiramate Background

1.3.1 Regulatory History

Topiramate, a monosaccharide sulfamate, was approved in December 1996, under the tradename Topamax® as an anti-epileptic drug (AED). It was approved for use in migraine prophylaxis in 2004.

Topiramate is classified as a Pregnancy Category C drug based on animal data and the risk/benefit considerations for the indicated populations if used during pregnancy.

Reviewer comment: Definitions of the FDA Pregnancy Categories are contained in Attachment 9.3 of this review.

1.3.2 Dosing and Indications

Topiramate is indicated for the following conditions (MHT Review, pg. 7):

- **Monotherapy epilepsy**: Initial monotherapy in patients ≥10 years of age with partial onset or primary generalized tonic-clonic seizures
- **Adjunctive therapy epilepsy**: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS)
- **Migraine**: Treatment for adults for prophylaxis of migraine headache

The recommended adult topiramate doses are:

- 400 mg/day given in two divided doses for monotherapy in epilepsy and for adjunctive therapy in primary generalized tonic-clinic seizures
- 200 to 400 mg/day in two divided doses for adjunctive therapy in epilepsy with partial onset seizures
- 100 mg/day in two divided doses for migraine prophylaxis

Topiramate is currently used off-label for weight loss purposes. The exact mechanism of action through which topiramate effects weight loss is not known. Hypothesized mechanisms of action include: increased energy expenditure secondary to anorexia;
reduction in the activity of salivary enzymes (which are partially responsible for taste); reduction in leptin and corticosteroid concentrations, and reduction in blood glucose and insulin concentrations.

**Reviewer comment:** The off-label use of topiramate for weight loss is particularly concerning, as it would presumably be prescribed to a wider population of women of childbearing age than for epilepsy and migraine. In addition, the practitioners prescribing topiramate for weight loss may not be as familiar with its safety profile as a neurologist, and therefore less likely to counsel patients on potential pregnancies.

1.3.3 Pharmacology

Topiramate is a sulfamate-substituted monosaccharide believed to block voltage dependent sodium channels, augment the activity of gamma-aminobutyrate at GABA-A receptors, antagonize the AMPA/kinase subtype of the glutamate receptor, and inhibit the carbonic anhydrase enzyme. Its effects are hypothesized to block the spread of seizures when they begin, although the exact mechanism of action is unknown1.

1.3.4 Pregnancy Labeling

Topamax® (topiramate) is classified as a pregnancy category C drug based on animal developmental reproductive and toxicology studies and the risk/benefit of use during pregnancy for the approved indications (benefit may outweigh the risk in pregnant patients with epilepsy or migraine). The pregnancy subsection of Topamax® labeling was revised on December 22, 2009, to include information on the effect of metabolic acidosis in pregnancy and the possible association with fetal harm, as topiramate use is associated with metabolic acidosis. In addition the nursing mothers subsection was updated to include limited human lactation data (MHT Review, pg. 7).

The current topiramate labeling with regard to pregnancy and breastfeeding is shown in its entirety in Attachment 9.1 of this review. An excerpt from the labeling is shown below.

### 8.1 Pregnancy

Pregnancy Category C.

Topiramate may cause serious adverse fetal effects, based on clinical and nonclinical data. Topiramate treatment is associated with 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) may be associated with decreased fetal growth,

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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.

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.

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/m2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

Pregnancy Registry

The North American Drug Pregnancy Registry has been established to collect information and provide scientific knowledge about safety and outcomes associated with pregnant women being treated with antiepileptic drugs. It is desirable that the experience from patients who are exposed to topiramate during pregnancy be reported to this registry. Such information can be reported to the North American Drug Pregnancy Registry by either a healthcare provider or the patient by calling 1-888-233-2334. Information about the North American Drug Pregnancy Registry can be found at http://www.massgeneral.org/aed/.

The remainder of the labeling describes the preclinical data.

The Sponsor has submitted a CBE supplement which makes the following changes to the “Pregnancy” section of labeling.
1.3.5 Preclinical Data

Multiple preclinical studies have documented adverse outcomes following prenatal exposure to topiramate. Preclinical studies of topiramate use during pregnancy are summarized in the topiramate labeling, as presented below:

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) of 400 mg/day on a mg/m² 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/m² basis) or greater during the organogenesis period of pregnancy. Embryo toxicity (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/m² 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/m² basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m² 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/m² basis) and reductions in pre-and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m² 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/m² basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m² basis) and higher.

**Reviewer comment:** The preclinical studies found an increase in craniofacial malformations and decreased birth weight at doses less than the relative recommended dose in humans, both of which are also observed in pregnancy registries and other pregnancy-related data in humans. These issues are discussed in more detail in later sections of the review.

2. ORAL CLEFT CBE Submission

2.1 2009 PREGNANCY REGISTRY UPDATE

2.1.1 North American AED Pregnancy Registry Background
The North American AED (antiepileptic drug) Pregnancy Registry was established at the Massachusetts General Hospital in Boston in 1996. This is a hospital-based registry in which any pregnant woman taking an antiepileptic (or anticonvulsant) drug for any medical condition may enroll at any time during her pregnancy. Women planning to become pregnant or whose pregnancy has been completed are not eligible to enroll (NAAED 2009 Update, pg. 6).

2.1.2 NAAED 2009 Update: Overview

Dr. Holmes of the NAAED registry noted that 2009 was the first year in which the NAAED provided each sponsor with the findings in pregnancies in which that company’s product was used, as monotherapy, in at least 50 enrolled and eligible pregnancies (2009 NAAED update, pg. 1).

The NAAED was organized into the following sections (2009 NAAED update, pg. 1):

1. Analyzable data available
2. Characteristics of enrolled women
3. List of major malformations identified
4. Prevalence of all malformations in comparison to the internal and external unexposed controls

These topics are presented, respectively, in the following sections of the review.

2.1.3 NAAED 2009 Update: Data Available

Reviewer comment: The NAAED 2010 update is reviewed in the following section of this document (Section 3), and encompasses the data in the 2009 update plus the additional cases which had accrued during the next year. Details of the NAAED 2009 update are included in this review, but the bulk of the reviewer commentary is contained in Section 3 (NAAED 2010 Update).

The findings are presented for pregnancies enrolled with an estimated date of delivery of January 1, 2009. Of the 445 analyzable pregnancy outcomes meeting this criteria, 265 (59%) were exposed to monotherapy and the remainder to polytherapy (2009 NAAED update, pg. 2). Polytherapy was defined as treatment with more than one AED during the first trimester. Other characteristics of the pregnancies within the 2009 NAAED update are presented in the table below.

Reviewer comment: The NAAED update states that it presents findings “for pregnancies enrolled with an estimated date of delivery of January 1, 2009. ” I believe that the sentence was intended to say pregnancies with a due date before January 1, 2009. The table below corroborates this assertion, as it describes the pregnancies summarized with due dates between January 1997 and December 2008.

FDA Table 1: Infants with first trimester monotherapy or polytherapy topiramate exposure within the NAAED Registry for estimated dates of delivery between January 1997 and December 2008 (Adapted from NAAED 2009 Update Table 1, pg. 6)
The NAAED registry categorizes enrollees as either “pure,” “traditional” or “unknown,” as defined below:

- **Pure Prospective:** Participants who enroll without having had the first trimester nuchal translucency screening test or either of the diagnostic tests, amniocentesis or chorionic villus sampling; also, the mother had not had the fetal survey by ultrasound at 16 to 20 weeks of gestation.

- **Traditional Prospective:** Participants who have enrolled after having had an amniocentesis, chorionic villus sampling test, nuchal translucency test, or an ultrasound after 15 weeks gestation.

- **Unknown:** Participants who have not been classified because data on the relevant prenatal tests are missing.

2.1.4 NAAED 2009 Update: Characteristics of Enrolled Women

The NAAED update reported that the characteristics of the women who reported having taken topiramate, as monotherapy, were similar to those of enrolled women who had taken other anticonvulsant drugs as monotherapy, after excluding those who had taken either phenobarbital or valproate (Table 2). There are also small differences between the women who had taken topiramate as monotherapy and the 340 unexposed women, who are the internal comparison group (NAAED Update, pg. 3).
In the first interview, each woman is asked to identify the specific medication she is taking. In the case of topiramate, most identified the brand as Topamax ® (NAAED 2009 Update, pg. 3).

The NAAED investigators commented that “now that more generic drugs are being marketed, a new strategy is being developed to help each enrolled woman to specify accurately whether she is taking the brand name drug or a generic version of the drug” (NAAED 2009 Update, pg. 3). The table below summarizes the characteristics of 1) women who received topiramate as monotherapy during the first trimester, 2) women who received other monotherapies (excluding phenobarbital and valproate) or 3) were internal controls unexposed to any AED.

FDA Table 2: Characteristics of eligible women by study group (Adapted from NAAED 2009 Update, Table 2, pg. 3)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Topiramate (n = 265)</th>
<th>Other monotherapies² (n = 3427)</th>
<th>Unexposed women (n = 340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Male</td>
<td>141 (54.0)</td>
<td>1698 (50.5)</td>
<td>173 (51.5)</td>
</tr>
<tr>
<td>Married</td>
<td>181 (73.9)</td>
<td>2027 (66.1)</td>
<td>323 (95.6)</td>
</tr>
<tr>
<td>Mother’s Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Grade 12</td>
<td>68 (27.6)</td>
<td>354 (15.0)</td>
<td>14 (4.1)</td>
</tr>
<tr>
<td>Some College, Junior Graduate</td>
<td>70 (28.5)</td>
<td>540 (22.9)</td>
<td>43 (12.7)</td>
</tr>
<tr>
<td>College Graduate (4-yr)</td>
<td>71 (28.9)</td>
<td>899 (38.1)</td>
<td>138 (40.8)</td>
</tr>
<tr>
<td>Post College</td>
<td>37 (15.0)</td>
<td>565 (24.0)</td>
<td>143 (42.1)</td>
</tr>
<tr>
<td>Maternal Age (mean, SD)</td>
<td>28.8 (5.7)</td>
<td>29.8 (5.3)</td>
<td>31.6 (4.3)</td>
</tr>
<tr>
<td>Gravida (mean, SD)</td>
<td>2.1 (1.4)</td>
<td>2.2 (1.4)</td>
<td>2.3 (1.3)</td>
</tr>
<tr>
<td>Mother Caucasian</td>
<td>241 (90.9)</td>
<td>3005 (87.7)</td>
<td>313 (92.3)</td>
</tr>
<tr>
<td>Father Caucasian</td>
<td>219 (82.6)</td>
<td>2886 (84.4)</td>
<td>311 (91.7)</td>
</tr>
<tr>
<td>Age at First Seizure (mean, SD)</td>
<td>17.6 (8.3)</td>
<td>17.4 (8.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Seizures During Pregnancy</td>
<td>65 (27.8)</td>
<td>858 (26.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Prenatal Vitamins or Multivitamins</td>
<td>141 (53.6)</td>
<td>2382 (70.2)</td>
<td>258 (76.1)</td>
</tr>
<tr>
<td>Folic acid Supplement</td>
<td>166 (63.4)</td>
<td>2408 (72.2)</td>
<td>240 (72.9)</td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>212 (80.0)</td>
<td>2998 (87.8)</td>
<td>317 (93.5)</td>
</tr>
<tr>
<td>&gt; None, &lt; ½ pack</td>
<td>18 (6.8)</td>
<td>155 (4.5)</td>
<td>14 (4.1)</td>
</tr>
<tr>
<td>≥ ½ pack, &lt; 1 pack</td>
<td>17 (6.4)</td>
<td>104 (3.0)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>≥ 1 Pack</td>
<td>12 (4.5)</td>
<td>131 (3.8)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Yes, but unknown</td>
<td>6 (2.3)</td>
<td>28 (0.8)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>204 (77.3)</td>
<td>2508 (73.4)</td>
<td>240 (71.0)</td>
</tr>
</tbody>
</table>
Reviewer comment: I reviewed the table above and found a number of differences in the topiramate and the other treatment groups. For example, more women in the topiramate group had less than 12 years of education (28% topiramate, 15% other monotherapy, 4.1% unexposed) and smoked at the rate of ½ to 1 pack per day (6.4% topiramate, 3% other monotherapy, 0.9% unexposed). In addition, the treatment groups differed with regard to alcohol intake during pregnancy; 2.3% of women in the topiramate group had five or more drinks per week, compared to 1.6% for the other monotherapy groups, and 4.1% in the unexposed women. In addition, fewer in the topiramate group were taking prenatal vitamins (53.6% vs 70.2% for other monotherapies, 76.1% unexposed) or folic acid supplements (63.4% for topiramate vs 72.2% for other monotherapies, 72.9% for unexposed).

2.1.5 NAAED 2009 Update: Major Malformations Identified

The 2009 NAAED update reported that 8 (3.0%) of the 265 topiramate monotherapy-exposed infants had malformations which were identified within the first five days after birth (Table 3). An additional two malformations were identified before 12 weeks of age.

FDA Figure 1: List of Confirmed Major Malformations (Adapted from NAAED 2009 Update, pg. 4)
SUBJECT DESCRIPTION OF EACH MAJOR MALFORMATION

Confirmed malformations diagnosed within first 5 days of life:

1110 hypospadias, penile;
3632 syndactyly of left hand, fingers 3-4;
3945 PDA, VSD and multiple hemivertebrae;
4376 bilateral hand anomalies: cleft hand (left); ulnar longitudinal deficiency (right); missing 2 fingers on each hand;
4797 cleft lip and palate, unilateral (right); microtia, right ear;
5206 cleft lip;
6889 cleft lip and palate, bilateral; hypospadias, coronal;
7176 cleft lip & palate

Confirmed malformations diagnosed after 5 days after delivery:

4568 duplicated ureter, vesicoureteral reflux;
5730 PDA in a full-term infant;
6718 metatarsus adductus bilateral;
7442 inguinal hernia, left

Legend: PDA = patent ductus arteriosus
VSD = ventricular septal defect

2.1.6 NAAED 2009 Update: Comparison to Internal/External Controls

The NAAED registry utilizes two control groups:

1. **Internal Control Group:** The internal "controls" were friends and family members of AED-exposed enrolled women. Through 2008, 340 women had enrolled in the internal control group.

2. **External Control Group:** The external controls were composed of infants surveyed at birth in a separate Active Malformations Surveillance Program at Brigham and Women’s Hospital (BWH) in Boston. This external group has been used for comparison in all malformations, as well as the frequency of specific malformations, such as isolated cleft palate in 206,244 births. The Surveillance Program at BWH uses the same inclusion/exclusion criteria and is administered by the same investigators as the NAAED Registry.

The NAAED investigators reported that compared to the External Comparison Groups identified at Brigham and Women’s Hospital, the frequency in the topiramate-exposed pregnancies was 3.0% for malformations identified in the first five days of life, a 1.8 fold increase (95% C.I. 0.9 to 3.6%) compared to controls. When expanded to the 12 malformations identified up to age 12 weeks of age, the relative risk was a 2.6 (95% CI:0.98 to 6.7) which was borderline significant statistically (pg. 3).

FDA Table 3: Prevalence of major malformations among infants exposed to topiramate in monotherapy during the first trimester. Includes both pure and traditional prospective
exposures. Comparison to both internal unexposed control group and external reference.
(Adapted from 2009 NAAED Report, Table 4, pg. 5)

<table>
<thead>
<tr>
<th></th>
<th>Topiramate (n = 265)</th>
<th>Other monotherapies (n = 3427)</th>
<th>Unexposed women (n=340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major anomalies diagnosed before 5 days of life</td>
<td>8 (3.0%) (1.4 to 5.7%)</td>
<td>61 (1.8%) (1.4 to 2.3%)</td>
<td>4 (1.2%) (0.4 to 2.8%)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.8 (0.91 to 3.6)</td>
<td>1.1 (0.83 to 1.4)</td>
<td>0.73 (0.27 to 1.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Topiramate (n = 265)</th>
<th>Other monotherapies (n = 3427)</th>
<th>Unexposed women (n=340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major congenital anomaly</td>
<td>12 (4.5%) (2.5 to 7.6%)</td>
<td>74 (2.2%) (1.7 to 2.7%)</td>
<td>6 (1.8%) (0.7 to 3.6%)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>2.6 (0.98 to 6.7)</td>
<td>1.2 (0.5 to 2.8)</td>
<td>Ref</td>
</tr>
</tbody>
</table>

1 Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists (LBH).
2 Excluding stillbirths and fetal deaths, unless autopsy performed.
3 Reference: Baseline prevalence rate of 1.62% in the Active Malformations Surveillance Program at Brigham and Women’s Hospital in Boston (n = 69,277) [Ref. 2], after excluding genetic disorders and chromosome abnormalities.
4 Reference: Internal control group (n=340), with diagnosis up to 12 weeks of age.

Comparison of the risk of a child with a major congenital malformation between the different AEDs studied in the NAAED registry.

Reviewer comment: The 2009 NAAED annual report did not contain a table similar to the one below (risk by AED monotherapy group) for oral clefts. However, this table was contained in the 2010 NAAED report and is shown in Section 3.5.1 of this review.

**FDA Table 4: Risk of Malformations among the different AED Treatment Groups of the NAAED Registry in 2009 (Adapted from NAAED 2009 Report, Table 5, pg. 7)**

<table>
<thead>
<tr>
<th></th>
<th>Topiramate (n = 296)</th>
<th>Lamotrigine (n = 1323)</th>
<th>Carbamazepine (n = 913)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child with Confirmed Major Congenital Anomaly</td>
<td>8 (2.7%) (1.2 to 5.1%)</td>
<td>17 (1.3%) (0.78 to 2.0%)</td>
<td>20 (2.2%) (1.4 to 3.3%)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.8 (0.93 to 3.6)</td>
<td>0.79 (0.49 to 1.3)</td>
<td>1.4 (0.9 to 2.1)</td>
</tr>
</tbody>
</table>

1 Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.
2 Excluding stillbirths and fetal deaths, unless autopsy performed.
3 Using the baseline prevalence rate of 1.62% in the unexposed external comparison group of newborn infants surveyed by the Active Malformations Surveillance Program at Brigham and Women’s Hospital in Boston (n = 69,277). [See ref. 3 and 4 on page 5.]

Reviewer comment: Further comments on the elevation of total MCM risk in the topiramate group, compared to other AEDs, are provided...
in Section 3 of this review which addresses the NAAED 2010 report. Briefly, this report concludes that an elevation in the risk of oral clefts and decreased birth weight is demonstrated for prenatal topiramate exposure, but that the risk of MCM with topiramate, as compared to other AEDs, does not reach the level at which a causal relationship can be inferred. Specifically, the confidence intervals for MCMs in the different AED groups overlap.

2.2 2010 NAAED Pregnancy Registry Update

2.2.1 NAAED 2010 Update: Overview

Reviewer comment: Details on the methodology and administration of the North American AED (NAAED) Pregnancy Registry are contained in Section 2.1 through 2.3 and Attachment 9.2 of this review.

This section of the review (Section 3) summarizes the annual report on pregnancy outcomes in the NAAED registry for women with an estimated due date falling between February 1997 and January 1, 2010. Briefly, the findings from 296 topiramate monotherapy-exposed pregnancies were available for analysis. Eleven (11) of these infants had major malformations (3.7%; 95% confidence interval [CI] 2.0 to 6.4%). Five (5) of the 389 unexposed internal controls, recruited by the NAAED registry had major malformations (1.29 %; CI 0.47 to2.8%). The Relative Risk (RR) for any type of malformation in these topiramate monotherapy-exposed infants in comparison to the internal reference group was 3.2 (95 CI 1.1 to 9.1). Of the 11 topiramate-exposed infants with malformations, eight had major malformations diagnosed before 5 days of age (2.7%; 95% CI 1.2 to 5.1%). In comparison to the baseline prevalence risk of 1.62% in the external comparison group of newborns at Brigham and Women’s Hospital (BWH) in Boston, the RR was 1.8 (95% CI 0.93 to 3.6).

Reviewer comment: For major congenital malformations, topiramate-exposed infants had a higher risk than in the external comparison group (women delivering at BWH hospital), but the confidence intervals on the relative risk did not exclude one (1.8 95% C.I. 0.9 to 3.6).

There were 4 topiramate-exposed infants born with cleft lip with or without cleft palate (CLP), two of whom had additional anomalies. (The NAAED investigators noted that there have been no topiramate-exposed infants with cleft palate only.) The RR of an infant being born with an oral cleft, including CLP, in comparison to the frequency of oral clefts in the external reference population of 206,244 infants born at BWH (0.7/1,000), was 21.3 (95% CI 7.9 to 57.1).

Reviewer comment: The strength of the safety signal for oral clefts in topiramate-exposed infants compared to infants born at the same hospital in which the registry is based is substantial (RR 21.3 [95% C.I. 7.9 – 57]).
2.2.2 NAAED 2010 Update: Data Available

The investigators identified analyzable 513 topiramate-exposed infants with an estimated date of delivery of January 1, 2010. Spontaneous abortions, mothers who withdrew and mothers who have been lost-to-follow-up were excluded as unanalyzable. (The investigators stated that miscarriages and stillbirths are documented if a copy of an autopsy is sent to the registry. The 513 infants included 214 born to women who took topiramate in polytherapy and 296 who took topiramate as monotherapy (NAAED 2010 Update, pg. 6).

2.2.3 NAAED 2010 Update: Characteristics of Enrolled Women

Of the 296 monotherapy-exposed infants, 184 (62%) were born to women who were “pure” prospective enrollees, 109 (37%) women were “traditional enrollees” (enrolled after having had some prenatal screening), and 3 had unknown status regarding prenatal screening. The characteristics of the pure prospective enrollees are shown in comparison to the infants exposed to the two other drugs used most often as monotherapy (lamotrigine and carbamazepine) in the table below (NAAED 2010 Update, pg. 6).

**FDA Table 5: Characteristics of “pure” prospective enrolled women who had taken either topiramate, lamotrigine, or carbamazepine in monotherapy during the 1st trimester** (Adapted from NAAED Table 1, NAAED 2010 Update, pg. 7)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Topiramate (n = 296)</th>
<th>Lamotrigine (n = 661)</th>
<th>Carbamazepine (n = 612)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Male</td>
<td>138 (51.2)</td>
<td>442 (52.0)</td>
<td>254 (50.2)</td>
</tr>
<tr>
<td>Married</td>
<td>217 (73.4)</td>
<td>777 (90.2)</td>
<td>428 (83.5)</td>
</tr>
<tr>
<td>Mother’s Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Grade 12</td>
<td>84 (31.1)</td>
<td>94 (12.1)</td>
<td>54 (18.6)</td>
</tr>
<tr>
<td>Some College, Junior Graduate</td>
<td>79 (28.3)</td>
<td>165 (21.3)</td>
<td>59 (20.3)</td>
</tr>
<tr>
<td>College Graduate (4-yr)</td>
<td>78 (28.6)</td>
<td>314 (40.5)</td>
<td>112 (38.5)</td>
</tr>
<tr>
<td>Part College</td>
<td>38 (13.6)</td>
<td>202 (26.1)</td>
<td>66 (22.7)</td>
</tr>
<tr>
<td>Maternal Age (mean, SD)</td>
<td>28.7 (5.6)</td>
<td>30.0 (5.9)</td>
<td>28.7 (5.1)</td>
</tr>
<tr>
<td>Gravida (mean, SD)</td>
<td>2.1 (1.0)</td>
<td>2.0 (1.3)</td>
<td>2.2 (1.2)</td>
</tr>
<tr>
<td>Mother Caucasian</td>
<td>269 (90.9)</td>
<td>770 (99.4)</td>
<td>449 (66.5)</td>
</tr>
<tr>
<td>Father Caucasian</td>
<td>243 (82.1)</td>
<td>732 (95.2)</td>
<td>441 (66.5)</td>
</tr>
<tr>
<td>Age at First Seizure (mean, SD)</td>
<td>17.4 (8.3)</td>
<td>17.8 (8.3)</td>
<td>16.9 (8.8)</td>
</tr>
<tr>
<td>Seizures During Pregnancy</td>
<td>71 (27.3)</td>
<td>236 (30.1)</td>
<td>124 (24.8)</td>
</tr>
<tr>
<td>Prenatal Vitamins or Multivitamins</td>
<td>154 (52.4)</td>
<td>529 (78.7)</td>
<td>318 (52.5)</td>
</tr>
<tr>
<td>Folic acid Supplement</td>
<td>182 (62.1)</td>
<td>675 (83.1)</td>
<td>344 (56.5)</td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>240 (81.1)</td>
<td>783 (91.2)</td>
<td>453 (88.5)</td>
</tr>
<tr>
<td>&gt; None, &lt; ½ pack</td>
<td>20 (6.8)</td>
<td>26 (3.2)</td>
<td>21 (4.1)</td>
</tr>
<tr>
<td>≥ ½ pack, &lt; 1 pack</td>
<td>18 (6.1)</td>
<td>20 (2.3)</td>
<td>13 (2.5)</td>
</tr>
<tr>
<td>≥ 1 Pack</td>
<td>13 (4.4)</td>
<td>22 (2.8)</td>
<td>21 (4.1)</td>
</tr>
<tr>
<td>Yes, but unknown</td>
<td>5 (1.7)</td>
<td>6 (0.7)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>230 (78.0)</td>
<td>644 (75.3)</td>
<td>359 (70.3)</td>
</tr>
<tr>
<td>Moderate (&gt; none, &lt; 5 drinks/week)</td>
<td>53 (18.0)</td>
<td>189 (22.1)</td>
<td>133 (26.0)</td>
</tr>
<tr>
<td>≥ 5 drinks/week</td>
<td>6 (2.0)</td>
<td>13 (1.5)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (2.0)</td>
<td>11 (1.3)</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td>Child’s Birthweight, gr (mean, SD)</td>
<td>3093 (351)</td>
<td>3382 (350)</td>
<td>3354 (622)</td>
</tr>
<tr>
<td>Child’s Length, cm (mean, SD)</td>
<td>49 (5)</td>
<td>51 (5)</td>
<td>51 (4)</td>
</tr>
<tr>
<td>Child’s Head Circumference, cm (mean, SD)</td>
<td>34 (1)</td>
<td>35 (2)</td>
<td>35 (3)</td>
</tr>
</tbody>
</table>

1 Excluding stillbirths and fetal death.

Reference ID: 2913276
2.2.4 NAAED 2010 Update: Major Malformations Identified

Of the 296 topiramate monotherapy-exposed infants, 11 (3.7%) had a major malformation. These are listed in the table below.

**FDA Table 6: Malformations in topiramate monotherapy-exposed infants (Adapted from Table 2, NAAED 201 Update, pg. 9)**

<table>
<thead>
<tr>
<th>CASE NUMBER</th>
<th>STATUS</th>
<th>MAJOR MALFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1110</td>
<td>pure</td>
<td>hypospadias, penile</td>
</tr>
<tr>
<td>3632</td>
<td>pure</td>
<td>3-4 syndactyly of left hand</td>
</tr>
<tr>
<td>3945</td>
<td>pure</td>
<td>patent ductus arteriosus; ventricular septal defect (large); atrial septal defect;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hemivertebrae (T6 and T9); horseshoe kidney; slow cognitive development</td>
</tr>
<tr>
<td>4376</td>
<td>pure</td>
<td>hand anomalies; split-hand deformity (Rt); longitudinal deficiency postaxial (L1);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>missing 2 fingers on each hand</td>
</tr>
<tr>
<td>4797</td>
<td>traditional</td>
<td>cleft lip and palate, unilateral; microtia (Rt)</td>
</tr>
<tr>
<td>5206</td>
<td>pure</td>
<td>cleft lip</td>
</tr>
<tr>
<td>6889</td>
<td>traditional</td>
<td>cleft lip and palate, bilateral; hypospadias, coronal</td>
</tr>
<tr>
<td>7176</td>
<td>pure</td>
<td>cleft lip &amp; palate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CASE NUMBER</th>
<th>STATUS</th>
<th>MAJOR MALFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>5730</td>
<td>pure</td>
<td>patent ductus arteriosus (diagnosed at 14 days of age in full-term infant)</td>
</tr>
<tr>
<td>6718</td>
<td>traditional</td>
<td>metatarsus adductus, bilateral</td>
</tr>
<tr>
<td>7442</td>
<td>pure</td>
<td>inguinal hernia, left (diagnosed at 32 days of age)</td>
</tr>
</tbody>
</table>

Legend: Pure = “pure” prospective enrollee, i.e. before having any prenatal screening. Traditional = traditional prospective enrollee after having had prenatal screening. * = malformation identified after infant was 5 days old, but before 12 weeks of age.

**Reviewer comment:** As reported by the NAAED investigators, the majority of women in the registry (85%) were taking AEDs for the treatment of seizures. The NAAED Annual Report did not specify the indications other than seizure control, but in an e-mail Dr. Holmes reported depression: 3%, migraine: 12% and a miscellaneous group, including pain, for 2%.

2.2.5 Comparison to Internal/External Controls

The 2010 NAAED Update carried out two analyses of malformations:
1. An analysis of the frequency of all major malformations;
2. An analysis of the frequency of any specific malformations which have occurred in 3 or more infants.

These analyses were carried out in all 296 women, including both pure and traditional enrollees. These analyses are described below (NAAED 2010 Update, pg. 16).
1. Analysis of frequency of all malformations: The findings in the infants of “pure” and traditional enrollees were combined for two sub-analyses: one comparing the frequency to the external control group and one comparing the frequency to the internal control group. The comparison to the external control groups is shown in Table 6 below.

**FDA Table 7: External Control Group Comparison: Major malformations diagnosed within 5 days of life among infants exposed to topiramate, lamotrigine, or carbamazepine during the first trimester. (Includes both pure and traditional prospective exposures) (Adapted from Table 3, NAAED 2010 Update, pg. 17).**

<table>
<thead>
<tr>
<th></th>
<th>topiramate (n = 296)</th>
<th>lamotrigine (n = 1323)</th>
<th>carbamazepine (n = 913)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child with Confirmed Major Congenital Anomaly¹,²</td>
<td>8 (2.7%) (1.2 to 5.1%)</td>
<td>17 (1.3%) (0.78 to 2.0%)</td>
<td>20 (2.2%) (1.4 to 3.3%)</td>
</tr>
<tr>
<td>Relative risk (95% CI)³</td>
<td>1.8 (0.93 to 3.6)</td>
<td>0.79 (0.49 to 1.3)</td>
<td>1.4 (0.9 to 2.1)</td>
</tr>
</tbody>
</table>

¹Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.
²Excluding stillbirths and fetal deaths, unless autopsy performed.
³Using the baseline prevalence rate of 1.62% in the unexposed external comparison group of newborn infants surveyed by the Active Malformations Surveillance Program at Brigham and Women’s Hospital in Boston (n = 69,277). [See ref. 3 and 4 on page 5.]

The comparison of AED–exposed infants to the internal control group is shown in Table 8 below:

**FDA Table 8: Internal Control Group Comparison: Prevalence of major malformations among infants exposed to topiramate, lamotrigine, or carbamazepine during the first trimester. Includes both pure and traditional prospective exposures (Adapted from Table 4, NAAED 2010 Update, pg. 9).**

<table>
<thead>
<tr>
<th></th>
<th>topiramate (n = 296)</th>
<th>lamotrigine (n = 1323)</th>
<th>carbamazepine (n = 913)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child with Confirmed Major Congenital Anomaly¹,²</td>
<td>11 (3.7%) (2.0 to 6.4%)</td>
<td>24 (1.8%) (1.2 to 2.6%)</td>
<td>20 (2.2%) (1.4 to 3.3%)</td>
</tr>
<tr>
<td>Relative risk (95% CI)³</td>
<td>3.2 (1.1 to 9.1)</td>
<td>1.3 (0.52 to 3.5)</td>
<td>1.2 (0.4 to 3.1)</td>
</tr>
</tbody>
</table>

¹Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.
²Excluding stillbirths and fetal deaths.
³Using the prevalence rate of 1.3% in the unexposed CONTROL group (n = 389; 5 malformed infants).
The NAAED investigators commented that these two tables demonstrate an increase of borderline significance in the absolute rate of major malformations. The relative risks in comparison to the two comparison populations were: 1) RR 1.8 (95% CI 0.9 to 3.6) in comparison to the unexposed population at Brigham and Women’s Hospital and 2) RR 3.2 (95% CI 1.1 to 9.1) in comparison to unexposed internal control group recruited by the North American AED Pregnancy Registry (NAAED 2010 Update, pg. 10).

Reviewer comment: The selection of a control group for pregnancies exposed to AEDs is difficult due to the fact that women who require AED treatment during pregnancy differ from women who do not have medical conditions or who have medical conditions which do not require treatment during pregnancy. However, the table above demonstrates an elevation in relative risk when compared to other AEDs (topiramate 3.2, lamotrigine 1.3, carbamazepine 1.2). Although the difference between the AED-treatment groups was not statistically significant, the elevation supports an increased pregnancy risk for topiramate compared to the other AEDs examined.

2.2.5.1 Analysis of Specific Malformations: Oral Clefts

The NAAED table below lists the specific malformations identified: 4 of the 11 were oral clefts, either cleft palate (CP), cleft lip (CL) or cleft lip and palate (CLP). The NAAED investigators reported that this number (4 in 296 infants or 13.5/1,000) represents a significant increase for this common malformation in comparison to the frequency of oral clefts in the external control group: 0.7/1,000 (NAAED 2010 Update, pg. 10).

The table below provides a comparison of oral clefts in three groups of infants, those exposed to either topiramate, lamotrigine or carbamazepine as monotherapy in the first trimester of pregnancy. The findings in pure and traditional enrollees have been combined.

*FDA Table 9: Comparison of oral clefts in infants exposed to topiramate, lamotrigine or carbamazepine (Adapted from Table 5, NAAED 2010 Update, pg. 10)*
The NAAED investigators stated that the table above shows a significant rate of occurrence of infants with oral clefts in infants exposed to either of three anticonvulsant drugs: carbamazepine, lamotrigine and topiramate. The investigators noted that previous case reports and small series of each of these anticonvulsant-exposed groups have reported these associations. However, the investigators stated that these sample sizes are larger than those reported previously. The investigators further commented:

“Finding a significant increase in the frequency of oral clefts in these three groups of anticonvulsant-exposed infants is surprising. We are not aware of any theoretical explanation of why three such different drugs should be associated with an increased frequency of the same outcome: oral clefts.”

Reviewer comment: The NAAED investigators stated that an analysis of topiramate polytherapy is currently ongoing and is planned to be submitted for publications. The results would also be available in the next NAAED annual report.

2.2.5.2 Analysis of Specific Malformations: Birth Weight

The analysis of the birth weight of infants exposed to topiramate as monotherapy during pregnancy showed a significant decrease of 215 grams (p < 0.001). The NAAED analysis showed that 9.7% of topiramate-exposed infants had a birth weight below 2,500 grams compared to 5.8% for other anticonvulsants (RR1.75; 95% CI 1.13 to 2.76; p = 0.013)(NAAED 2010 Update, pg. 10).

Reviewer comment: The NAAED investigators stated that a more detailed analysis of low birth weight, including an assessment of confounders such as cigarette smoking, is currently underway. The results are expected to be presented at the annual meeting of the Teratology society in June, 2010.

2.2.6 Other NAAED Observations

The NAAED investigators commented on results of another registry, the UK epilepsy registry, as published in a study by Hunt et al. (See Section 8.1 of this review).

Reference ID: 2913276
The NAAED investigators noted significant differences in the methodologies in the UK and NAAED pregnancy registries (including the lack of a control group in the UK registry), but stated that despite this difference, the only published findings in topiramate-exposed pregnancies have been among the infants born to women enrolled in the UK Epilepsy and Pregnancy Registry. The UK registry publication reported the findings in 70 infants exposed to topiramate as monotherapy. Three infants (3/70; 4.2%) in the UK registry had major malformations: 1) cleft lip and palate (two infants); 2) hypospadias. The NAAED investigators stated that it was “unfortunate” that the severity of the hypospadias was not specified in the Hunt et al, UK publication, adding that most affected infant boys have a mild glandular type of hypospadias, which the investigators noted is excluded as a minor anomaly with “no surgical, medical or cosmetic importance” within the NAAED registry (NAAED 2010 Update, pg. 11).

**Reviewer comment:** The Hunt et al. publication on data from the UK registry is discussed in more detail Section 7.1 of this review.

Dr. Kapcala of the DNP contacted Dr. Holmes, the lead investigator at the NAAED registry and asked for additional information on the doses of topiramate in infants with cleft lip/palate. Dr. Holmes replied (via e-mail) by forwarding the table below in which these 11 malformed infants are listed. Dr. Holmes clarified that the table is subdivided by the ages at which these diagnoses were established. This reflects the two different comparison groups used. Those identified at birth can be compared to the findings in the Active Malformations Surveillance Program at Brigham and Women’s Hospital, where malformations are identified between birth and 5 days of age. The second time period (after 5 days and up to 12 weeks of age) can be compared to the internal comparison group. The postpartum interview with the mother is conducted between 8 and 12 weeks after the infant’s birth.

FDA Table 10: Prenatal Topiramate Dosing for Infants born with Cleft Lip/Palate within the NAAED Pregnancy Registry (Supplied by Dr. Holmes of the NAAED Pregnancy Registry)

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Dose (mg) 1st trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx &lt;5 days after delivery</td>
<td>1110 1200</td>
</tr>
<tr>
<td>3632 60 -&gt; 45 @ 13 wks</td>
<td></td>
</tr>
<tr>
<td>3945 100</td>
<td></td>
</tr>
<tr>
<td>4376 200</td>
<td></td>
</tr>
<tr>
<td>4797 200</td>
<td></td>
</tr>
<tr>
<td>5206 200</td>
<td></td>
</tr>
<tr>
<td>6889 400</td>
<td></td>
</tr>
<tr>
<td>7176 100</td>
<td></td>
</tr>
<tr>
<td>Dx &gt;5 days after delivery</td>
<td>5730 150</td>
</tr>
<tr>
<td>6718 50</td>
<td></td>
</tr>
<tr>
<td>7442 200</td>
<td></td>
</tr>
</tbody>
</table>
3. DECREASED BIRTH WEIGHT CBE SUBMISSION

3.1 Rationale for Labeling Change

In October 2010, the sponsor submitted a Changes Being Effected (CBE) supplement with labeling describing a decrease in birth weight in children with prenatal exposure to topiramate. The sponsor stated that the decision was based on data from the North American Antiepileptic Drug (AED) Pregnancy Registry. The sponsor noted that “In addition, published results from an epidemiological study also reported low birth weights in pregnancies with prenatal topiramate exposure.”

Reviewer comment: The epidemiologic study referred to in the sentence above is a publication based on data from the Israeli Teratogen Information Service (Ornoy et al. 2008). This study is discussed in more detail in Section 7.3 of this review.

The sponsor explained that based upon its mechanism of action, they believe it is biologically plausible that topiramate would decrease birth weight in infants with prenatal exposure. The sponsor stated that weight loss associated with the use of topiramate, which is known to inhibit carbonic anhydrase (CA), has been observed in clinical trials of epilepsy and migraine patients (IB Topiramate 2008) and in obese patients. The sponsor noted that inhibition of carbonic anhydrase enzymes is involved in several steps of de novo lipogenesis. This mechanism has been proposed as a possible treatment of obesity, and the sponsor hypothesized that the low birth weight observed with topiramate could be caused by the same mechanism (Low Birth Weight CBE, pg. 7-8).

The sponsor asserted that results for topiramate from the North American AED Pregnancy Registry demonstrated a signal for a reduction in birth weight among children exposed to topiramate in utero, as did results from an epidemiological study reported in the scientific literature (Ornoy 2008). The reports highlighted that the birth weights of children exposed to topiramate monotherapy appeared to be less than those of children who were exposed to other AED monotherapies and to the mean birth weights of term children not exposed to AEDs (Low Birth Weight CBE, pg. 7).

3.1.1 NAAED Registry Data

The sponsor stated that they received a report on topiramate and low birth weight from the North American AED Pregnancy Registry in 2009, and results from the Registry were presented at the 50th Annual Meeting of the Teratology Society in June 2010 (Hernandez-Diaz 2010).

3 The sponsor referenced the “Topiramate birth weight report 2009” and “Hernandez-Diaz 2010” in support of this assertion.
Demographic information was available from the pregnancy registry for 269 subjects treated with topiramate monotherapy during pregnancy and for 360 internal control subjects (friends and family members of the topiramate-exposed subjects) not exposed to any AED, as of 1 May 2009. The sponsor observed that there were differences in sociodemographic characteristics of women treated with topiramate monotherapy compared to the unexposed internal controls, specifically that women using topiramate were more often single and less educated, a higher proportion smoked, and fewer had used prenatal vitamins or folic acid supplements.

In the NAAED registry data, prenatal exposure to topiramate monotherapy was associated with a 302 gram lower birth weight compared to the non-exposed reference group, \((P<0.001)\). The prevalence of low birth weight (<2,500 grams) in liveborn singletons without major malformations was 9.7% for topiramate and 3.2% for controls (Relative Risk [RR] 3.27, 95% Confidence Interval [CI]: 1.57-6.80). Adjustment for potential confounders reduced the association, but it remained significant (adjusted RR 2.97, 95% CI: 1.38-6.40). Restriction to non-smokers and non-drinkers further reduced the RR to 1.99 (95% CI: 0.77-5.16). Mean gestational age was similar for the topiramate group and the unexposed controls (39.0 weeks and 39.2 weeks, respectively; Topiramate birth weight report 2009)(Low Birth Weight CBE, pg. 9).

Similar findings were observed in the analyses of NAAED data reported in a study by Hernandez-Diaz (2010), which included 20 additional topiramate monotherapy patients and 12 additional control subjects compared to the Registry report. Compared to the non-exposed reference group, prenatal exposure to topiramate monotherapy was associated with a 307 gram lower birth weight \((P<0.001)\). The prevalence of low birth weight (<2,500 grams) in liveborn singletons without major malformations was 9.8% for topiramate and 3.6% for controls (RR 2.7, 95% CI: 1.4-5.1; Hernandez-Diaz 2010)

3.1.2 Ornoy et al. Study Data

The sponsor noted that results from an epidemiological study in Israel (Ornoy 2008) showed evidence of a reduction in birth weight among children exposed to topiramate in utero. In this study, the authors described the pregnancy outcomes of women who contacted the Israeli Teratogen Information Service (TIS) between January 1996 and December 2006 in regard to exposure to topiramate. There were 52 pregnancies with in
utero topiramate exposure (29 monotherapy, 23 polytherapy); 41 resulted in liveborn infants (11 abortions). In a control group consisting of women who contacted the TIS during the same time period and were exposed to non-teratogenic agents, there were 212 pregnancies with 198 liveborn infants. Birth weight was significantly lower in the topiramate group compared to the control group (median weights were 2932 grams and 3300 grams, respectively; p=0.024). There was no difference in gestational age at birth (40 and 39 weeks for topiramate and control groups, respectively) and rate of prematurity. The authors concluded that topiramate reduced birth weight without decreasing gestational age at delivery (compared to control subjects exposed to non-teratogenic agents during pregnancy), but did not seem to increase the risk for structural defects (Low Birth Weight CBE, pg. 9).

**Reviewer comment:** As noted in more detail in Section 8 (Conclusions and Recommendations) of this review, I agree with the sponsor’s assessment that decreased birth weight in infants with in utero exposure to topiramate deserves to be included in the topiramate labeling.

### 3.2 Sponsor-Proposed Labeling Change

The sponsor made the following addition (shown in the underlined text) to the topiramate labeling.
**Reviewer comment:** Finalized pregnancy labeling, created with input from the sponsor, DNP and MHT, is contained in Section 9.4. For the reasons discussed in section 8.1 of this review, low birth weight has not been added to the label.

4. AERS CASE SERIES

4.1 AERS Case Series: Background

In March 2010, the DMEP requested that the FDA’s Dr Sonia Tabacova (DPP) review a search of the AERS database for adverse pregnancy outcomes following prenatal exposure to topiramate and phentermine. The consult request asked that the two drugs be examined separately and when co-administered (Qnexa ®)(AERS Case Series, pg. 2).

4.2 AERS Case Series: Summary Characteristics

The AERS search revealed a total of 115 spontaneous reports of adverse fetal, neonatal and/or postnatal events associated with administration of topiramate as a monotherapy to pregnant women. Of these 115 reports, 39 reports were excluded from this review because of the following reasons: duplicate reports (n=25); irrelevant reports (topiramate exposures not gestational/ prenatal) (n=13); and outcome of pregnancy not reported (n=1).

The table below summarizes the characteristics of the remaining 76 cases (OSE Review, pg. 2-3).

**FDA Table 11: Summary of 76 Pregnancy-Related Case Report in the AERS database for Topiramate** (Adapted from OSE review text, pg. 2-4)

<table>
<thead>
<tr>
<th>Year Case Reported</th>
<th>1997 through 2009 (incl.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of Origin</td>
<td>23 (~30%) from the US, 56 (70%) from other countries</td>
</tr>
<tr>
<td>Literature Source</td>
<td>22 (~30%) were from literature sources</td>
</tr>
<tr>
<td>Reporter</td>
<td>62 (~80%) reported by health professionals</td>
</tr>
<tr>
<td>Indication</td>
<td>Information on indication available in 51 (67%) of reports</td>
</tr>
<tr>
<td>Topiramate Dose</td>
<td>Topiramate dose was reported in 45 of 76 cases</td>
</tr>
<tr>
<td></td>
<td>- ≤ 200 mg/day in 29 of 45 reports (64%)</td>
</tr>
<tr>
<td></td>
<td>- &gt; 200 to 400 mg/day in 9 cases (20%)</td>
</tr>
<tr>
<td></td>
<td>- &gt; 400 to 600 mg/day – in 4 cases (9%)</td>
</tr>
<tr>
<td></td>
<td>- &gt;600 mg/day – in 3 cases (7%)</td>
</tr>
<tr>
<td>Timing of Prenatal</td>
<td>Timing and duration of topiramate use was available in 46 (60%)</td>
</tr>
</tbody>
</table>
Exposure reports:
• Most (40/46, 87%) reported exposure in the first trimester
• ~Half (21 of 40) of the reports noted that topiramate use was continued through the entire duration of pregnancy
• Exposures starting after the 1st trimester were not common (6 of 46, or 13%)

Concomitant Medications
Concomitant drugs were reported in only 5% of the cases (4 of 76), including:
• Carbamazepine (in 2 cases, both during the 1st trimester)
• Lamotrigine (in 1 case, prior to the pregnancy)
• Chemotherapy/radiation therapy (in 1 case, 2 months before conception)

Concurrent Pregnancy Complications
Concurrent pregnancy complications were reported in 3 cases (3/76, 4%)
• Premature rupture of membranes (N=2)
• Amnioitis (N=1)

Pre-existing Maternal Disease
1 report noted pre-existing maternal illness (brain tumor, surgically removed before conception)

**Reviewer comment:** In her review, Dr. Tabacova commented that the fact that most of the reports (over 80%) were reported by health professionals strengthened the credibility of the case series. She also stated that because most mothers in the series did not have concomitant medications or medical conditions, there was uniformity of maternal health background, reducing potential confounding variables. However, this uniformity assumes complete and accurate reporting within the case reports, which would be atypical for AERS reports. Dr. Tabacova also noted that in the majority of reports (87%) topiramate exposure occurred in the first trimester, the most vulnerable period of embryofetal development.

As per Dr. Tabacova’s review, maternal information was poorly reported within the case series. For example, maternal age was reported in less than a third of the cases (21 of 76), and information about gravidity and parity was available in less than one sixth of the reports (13 of 76). According to these limited data, maternal age between 20 and 30 years was prevalent (in 14 of 21 cases); the proportion of primigravida and primipara was one third, and about one half of mothers were multiparous (3 or more births)(AERs review, pg. 4).

Information on pregnancy outcome was available in the majority of the reports (70 of 76, or 92%). Elective abortions due to fetal malformations comprised 13% of the reported outcomes (9 of 70). The rest of the outcomes were live births (61, or 87%). Gestational age at birth was reported in less than a half of these (27 births), including 19 term- and 8 preterm births. Neonatal gender (reported in 46 cases) was 56% males (26 of 46) and 44% females (20 of 46)(AERs review, pg. 7).

**Congenital malformations** were reported in 93% of all AE reports (71 of 76). The remaining 7% (5 of 76) reported postnatal adverse events without structural
malformations. Thus, congenital malformations were almost exclusively the reason for adverse event reporting in association with topamax use in pregnancy.

TDA Table 11: Distribution of Adverse Events in the AERS Case Series (Adapted from AERS review, pg. 8)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>N reported (Percent of all AE reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital malformations:</strong></td>
<td></td>
</tr>
<tr>
<td>- Non genetic</td>
<td>67</td>
</tr>
<tr>
<td>- Genetic syndromes</td>
<td>4</td>
</tr>
<tr>
<td><em><em>Postnatal AE</em> (no malformations)</em>*</td>
<td>5 (6.6%)</td>
</tr>
</tbody>
</table>

The 71 cases of congenital malformations included 4 cases of malformation syndromes of genetic origin all confirmed by karyotype analyses: Edward's syndrome (Trisomy18), Di George’s (chromosome 22 q11.2 deletion syndrome, also known as conotruncal anomaly face syndrome, congenital thymic aplasia), Cri-du-chat (also known as chromosome 5p deletion syndrome), and Prader-Willi (chromosome 15 q11-13 deletion syndrome that involves obesity, decreased muscle tone, decreased mental capacity, and hypogonadism). Dr. Tabacova stated that these cases were excluded from further review because genetic birth defects could arise independently of prenatal drug exposures. Out of the remaining 67 cases, 3 did not specify the type of malformations. Therefore, the following table of the reported malformations was based on 64 case reports (AERS review, pg. 18).

FDA Table 12: Congenital malformations’ spectrum and reporting frequency (Adapted from AERS Review, pg. 3)

<table>
<thead>
<tr>
<th>Type of malformation</th>
<th>N reported (Percent of all malformation cases)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total reported malformation cases</td>
<td>67 (excluding congenital genetic syndromes)</td>
</tr>
<tr>
<td>- Malformations not specified</td>
<td>3</td>
</tr>
<tr>
<td>- Malformations specified</td>
<td>64</td>
</tr>
<tr>
<td><strong>Craniofacial</strong></td>
<td></td>
</tr>
<tr>
<td>- Cleft lip and/or palate</td>
<td>11</td>
</tr>
<tr>
<td>- Facial dysmorphism (incl. auricular dysplasia)</td>
<td>6</td>
</tr>
<tr>
<td>- Micrognathia</td>
<td>4</td>
</tr>
<tr>
<td>- Skull deformation and ossification abnormalities</td>
<td>3</td>
</tr>
<tr>
<td>- Macroglossia</td>
<td>1</td>
</tr>
<tr>
<td><strong>Skeletal</strong></td>
<td>19 /64 (29.9%)</td>
</tr>
</tbody>
</table>
Dr. Tabacova asserted that the malformations reported to AERS displayed a distinctive and consistent pattern. The most common malformation in the case series were craniofacial (predominantly oral clefts, but also facial and skull dysmorphism, micrognathia), as well as skeletal limb defects (long bones’ and phalangeal hypoplasia, aplasia or deformities, including adactyly, brachydactyly, syndactyly, radius or femoral hypoplasia, hip dysplasia, talipes). Both craniofacial and skeletal limb malformations were each reported in about 30% of the reviewed 64 malformation reports.

**Reviewer comment:** The NAAED registry also found that oral clefts were the predominant form of malformation observed following prenatal topiramate exposure. This could be considered an independent replication of this finding. It should be noted,
however, that there is also potential overlap between the cases within AERS and the women enrolled in the NAAED registry, which would not represent an independent replication.

Cardiovascular (predominantly ventricular or atrial septal defects) were the third most frequently reported group of malformations (23% of reports). The reporting rate of these defects was not higher in the premature births (1 of 8), or in the low body weight infants (1 of 14), which suggests that they cannot be attributed to neonatal immaturity. Less frequently reported (in 14% of the reports) were genitourinary abnormalities (hypospadias, labial adhesions, ureteral malformations, hydronephrosis, congenital nephrolithiasis) and CNS malformations in 12% of reports (neural tube closure defects, i.e., spina bifida, and brain hypoplastic or aplastic lesions, i.e., microcephaly, microgyria, corpus callosum aplasia, hydrocephaly). Gastrointestinal and pulmonary malformations were rarely reported (single cases)(AERS review, pg. 4).

Reviewer comment: The DNP has consulted Dr. Holmes of the NAAED registry periodically regarding pregnancy-related drug safety issues. When Dr. Mary Roberts (the FDA’s primary Qnexa reviewer) asked Dr. Holmes about combining individual adverse outcomes, he stated that he believes it is appropriate to combine cleft lip and palate abnormalities, but that he would not combine cleft lip/palate and other (non-facial) skeletal abnormalities4.

Dr. Tabacova found it particularly note-worthy that an uncommon abnormality (congenital nephrolithiasis) was reported in association with topiramate prenatal exposure in one of the reports. That it was likely for this association to be causal is supported by the ability of topiramate, as a carbonic anhydrase inhibitor to “create a physiological environment that increases the risk of renal stone formation” (From Topiramate labeling, under “Other Drug Interactions”).

4.3 AERS Case Series: Adverse Outcomes other than Congenital Malformations

Dr Tabacova noted the following adverse outcomes which were not considered a congenital malformation (AERS review, pg. 5):

1. **Intrauterine growth retardation** was reported in addition to other pathology in 14 (23%) of 61 live births. It was not reported as an independent adverse event.

2. **Postnatal adverse events** were reported in 9 of 61 live births. In 5 of these 9 cases there were no congenital malformations; the reported events included mental and physical developmental delays (in 2 cases, one of which also involved maternal use of cannabis during pregnancy); convulsions (infantile spasms, or West’s syndrome) in 1 case; muscle hypotonia and feeding difficulties (1 case); and strabismus (1 case). In the remaining 4 cases, postnatal adverse events arose in association with accompanying congenital malformations. These cases included 2 cases of mental and physical developmental delays with accompanying CNS or cardiovascular malformations and 2 cases of infant deaths (one case of intra-

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4 This information was conveyed by Dr. Len Kapcala of the DNP.

Reference ID: 2913276
partum death from cardiac and pulmonary complications in a premature infant with multiple malformations; and one death during the first week of life in an infant with a major cardiovascular malformation (one ventricle) whose mother had been treated with another antiepileptic drug, lamotrigine, prior to pregnancy and prior to topiramate.

4.4 AERS Case Series: Topiramate Dose and Timing

In nearly all congenital malformations cases, topiramate gestational exposure (data available in 42 cases) started in the 1st trimester of pregnancy (37 of 42, or 88%), and, in half of these, did not continue beyond the 1st trimester. In all cases of postnatal AEs, topiramate administration covered the entire pregnancy, in some cases continuing even beyond birth through lactation. It is of note that the only case in which topiramate administration started late in gestation (in the 3rd trimester) presented with hypotonia and feeding difficulties (i.e., clinical signs attributable to the pharmacological effect of the drug), but no other pathology (AERS review, pg. 5).

Reviewer comment: As Dr Tabacova also noted, the data suggest that structural congenital malformations generally occurred with topiramate exposures involving the 1st trimester of pregnancy, while postnatal CNS manifestations and developmental delays were associated with exposures that continued beyond the 1st trimester. This pattern would be expected for teratogen exposure during these respective time periods in pregnancy, and this finding supports a biologic plausibility for a causal association.

Dr. Tabacova reported that topiramate dose (in the reported dose range of <200 - >600 mg/day) did not appear to affect the type of AEs or the rate of their reporting. The adverse events reported at daily doses of 200 mg or less were not different by type and reporting frequency from those at daily doses of over 200 or over 400 mg. However, the small number of cases treated with doses greater than 400 mg/day (n=7) do not allow a definitive conclusion (AERS review, pg 6).

With regard to dose-response, Dr. Tabacova reported that the number of reported cases and the malformation pattern are similar across topiramate dose ranges, including doses at or below 100 mg/day.

Topamax – Malformation pattern by dose (source: FDAs AERS) (Prepared by Dr. Sonia Tabacova)

Information about dose was available in 44 cases of congenital malformations reported to FDAs AERS in association with topamax monotherapy in pregnancy. These cases are stratified according to the dose as follows:
- Up to 100 mg/day: 8 cases;
- >100 – 200 mg/day: 16 cases;
- >200 – 400 mg/day: 9 cases;
- >400 mg/day: 7 cases.
Within these dose ranges, the malformation profile was as follows:

<table>
<thead>
<tr>
<th>Topamax Dose (mg/day)</th>
<th>Up to 100</th>
<th>&gt;100 – 200</th>
<th>&gt;200 – 400</th>
<th>&gt;400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N reported cases of congenital malformations</td>
<td>8</td>
<td>16</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Malformation types, N (% of total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Craniofacial</td>
<td>3 (37.5%)</td>
<td>3 (19%)</td>
<td>2 (22%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>- CNS</td>
<td>2 (25%)</td>
<td>1 (6%)</td>
<td>2 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>- Cardiovascular</td>
<td>2 (25%)</td>
<td>5 (31%)</td>
<td>0</td>
<td>2 (28%)</td>
</tr>
<tr>
<td>- Musculoskeletal</td>
<td>2 (25%)</td>
<td>6 (37.5%)</td>
<td>1 (11%)</td>
<td>2 (28%)</td>
</tr>
<tr>
<td>- Genitourinary</td>
<td>0</td>
<td>2 (12%)</td>
<td>3 (33%)</td>
<td>1 (14%)</td>
</tr>
</tbody>
</table>

Based upon the table above, Dr. Tabacova concluded that the number of malformation case reports and the pattern of malformations reported to AERS in association with topiramate monotherapy in pregnancy at doses of up to 100 mg/day are no different from those reported with doses of over 100, 200, or over 400 mg/day (AERS reviews, pg. 19).5

**Reviewer comment:** Although the crude number of cases is highest in one of the lower dose ranges, without denominator information at these dose levels it is not possible to assess whether the risk is elevated at higher dose levels. In addition, dose-response should ideally be assessed in a fixed dose study. Otherwise, the analysis is confounded by disease severity (i.e. patients with more severe disease require higher doses for treatment).

### 4.5 AERS Case Series: Confounding Factors

Dr Tabacova listed the following factors as potential confounders (AERS review, pg 5):

1. **Concomitant drug use** was reported in only 4 cases: 2 involving carbamazepine (1st trimester), 1 – lamotrigine prior to pregnancy, and 1 – chemo- and radiation therapy 2 months before conception. The types of malformations reported in these cases (i.e., hemangioma and diaphragmatic hernia in the 2 carbamazepine cases; a single heart ventricle in the lamotrigine case; and a genetic malformation

5 The percentages listed in Dr. Tabacova’s table appear to be based on the total N reported cases of congenital malformations, rather than the N related to malformation types (N=9 for Topamax dose up to 100 mg/day, N=16 for dose > 100-200 mg/day, N=8 for dose> 200-400 mg/day, and N=8 for dose > 400 mg/day). When the latter is used as the denominator, the percentages are slightly different (for example for doses up to 100 mg/day, 33% for craniofacial malformations, 22% for CNS, 22% for cardiovascular, and 22% for musculoskeletal).
syndrome Cri du chat in the pre-pregnancy chemo-and radiation exposure) were
different from the malformation pattern seen with topiramate alone.

2. Smoking, alcohol consumption and recreational drug use were rarely reported (in
6, 5 and 1 case, respectively). The types of malformations reported in these
particular cases were not different from the rest of the reported cases.

3. Maternal demographic characteristics (age, gravidity, parity) were reported in
insufficient number of reports to allow for a meaningful interpretation.

4. Gestational age at birth could confound topiramate association with
cardiovascular malformations since cardiac septal defects are known to be more
common among immature or pre-term infants. The present case series included 8
premature births (37 weeks gestation or less) and 14 cases of intrauterine growth
retardation or small for gestational age babies. In these cases, cardiovascular
malformations were not seen more frequently than in the rest of the cases (i.e., 1
case of atrial septal defect in 8 AE reports in premature infants; and 2 cases - of
atrial and of a ventricular septal defect in 14 AE reports of intrauterine growth
retardation and small for gestational age infants, as compared to 15 cardiovascular
malformations in the total of 76 AE cases reviewed.

5. TOPIRAMATE DATAMINING

In March 2010, as part of the review of Qnexa®, the DNP requested that the Office of
Epidemiology and Surveillance (OSE) perform a datamining analysis comparing reports
of malformations following prenatal topiramate exposure to reports for four other AEDs:
valproic acid, lamotrigine, oxcarbazepine and zonisamide. The results for topiramate are
shown in the table below, along with pertinent results for other AEDs for comparison.

FDA Table 13: Malformations with topiramate use reported to the AERS database with a
datamining score of EB05 of 2 or more (Adapted from OSE Datamining Results)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Malformation</th>
<th>N</th>
<th>EB05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>Cleft lip and palate</td>
<td>25</td>
<td>36.03</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Cleft lip</td>
<td>20</td>
<td>19.99</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Cleft palate</td>
<td>22</td>
<td>10.47</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Cleft lip and palate</td>
<td>54</td>
<td>10.32</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Cleft palate</td>
<td>45</td>
<td>16.55</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Cleft lip</td>
<td>9</td>
<td>4.92</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Cleft palate</td>
<td>33</td>
<td>15.26</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Cleft lip</td>
<td>16</td>
<td>13.34</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Cleft lip and palate</td>
<td>8</td>
<td>6.75</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Cleft palate</td>
<td>4</td>
<td>5.28</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Congenital musculoskeletal anomaly</td>
<td>7</td>
<td>2.01</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Congenital anomaly</td>
<td>31</td>
<td>2.07</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Congenital hydronephrosis</td>
<td>5</td>
<td>2.17</td>
</tr>
</tbody>
</table>
**Reviewer comment:** In the analysis above, oral clefts with prenatal exposure to topiramate is an outlier (EB 05 36.03) compared to oral clefts with exposure to other AEDs.

### 6.6 AERS Case Series: Reviewer Conclusions

Dr. Tabacova concluded that the reported malformations display a distinctive and consistent pattern. Dominating are craniofacial malformations (predominantly oral clefts) and skeletal limb defects (long bones and phalangeal), followed by cardiovascular malformations (predominantly ventricular and/or atrial septal defects). The combination of skeletal, craniofacial and cardiovascular malformations is the most frequently reported combination in the multiple malformation cases.

The presence of a pattern in the reported congenital malformations and their similarity to those seen in experimental animals prenatally exposed to topiramate indicates that the reported malformations in humans are not random and their association with maternal exposure to topiramate during gestation is plausible (AERS review, pg. 8).

**Reviewer comment:** I agree with Dr. Tabacova that the malformations in the AERS case series do appear to form a pattern around a few organ systems, rather than a “scatter shot” listing of unrelated adverse events. I also agree that the fact that the malformations in the case series are similar to those seen in animal studies supports the biologic plausibility of topiramate precipitating congenital malformations.

### 6. MATERNAL HEALTH TEAM CONSULT

#### 6.1 MHT Review: Overview

In March 2010, the Division of Metabolic and Endocrine Products (DMEP) consulted the FDA’s Maternal Health Team (MHT) to provide input on the following pregnancy-
related issues concerning Qnexa®, a combination drug for weight loss containing phenteramine and topiramate (MHT Review, pg. 4).

- Qnexa® pregnancy and nursing mothers labeling, including the pregnancy category classification
- Development of a pregnancy exposure registry
- Consideration of a lactation study
- Development of a pregnancy prevention plan.

6.2 MHT Review: Reproductive Risk Databases

As part of their review, the MHT reviewers consulted various reproductive risk databases for information on both phenteramine and topiramate. The MHT reviewers noted that there was limited human pregnancy data within the reproductive risk databases. This information is summarized below (MHT Review, pg. 27):

1. The REPROTOX® teratogen database described topiramate’s reproductive risk as follows:

   “Topiramate produces abnormal pregnancy outcome in experimental animals. Human case reports and case series have identified both normal and abnormal pregnancy outcome after topiramate exposure, without a clear increase in the incidence of congenital anomalies.”

2. TERIS® is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women characterized the reproductive risk of topiramate reproductive as shown below:

   “The magnitude of teratogenic risk to a child born after exposure during gestation is minimal to small and the quality and quantity of data on which the risk estimate is based is limited to fair.”

6.3 Pregnancies in the Qnexa® Development Program

**Reviewer comment:** The primary limitation in examining topiramate within the Qnexa® development program is the fact that Qnexa® is a combination drug which includes phenteramine. Phenteramine is classified as Pregnancy Category C, which is a significant confounder in evaluating malformations. The Qnexa® data is included here for thoroughness, but this limitation should be considered in the consideration of the information.

The MHT consult reported that 34 pregnancies occurred in clinical trials with Qnexa® despite a study requirement for females of childbearing potential to use a double-barrier method of contraception, a stable hormonal contraception plus a single barrier method, or have a tubal ligation, while on study drug. Fourteen of the pregnant women reported
using an oral contraceptive along with a single barrier method of contraception (usually a condom); 18 of the women reported using a double barrier method of contraception (MHT Review, pg. 15).

**Reviewer comment:** The finding of multiple pregnancies despite instructions to use two forms of birth control is consistent with previous evidence, in either study protocols or in product labeling, that these instructions are not strictly followed by patients.

Urine pregnancy tests were obtained at screening, randomization, and dose titration and then every 4 weeks at regular treatment clinic visits. Of the 34 pregnancies during the QNEXA development program, there were 18 liveborn infants (the remainder included 10 elective terminations, 3 spontaneous terminations, 1 ectopic pregnancy, 1 pregnancy with an unknown outcome and one which was ongoing as of May 2010). The majority of pregnancies occurred in the PHEN/TPM 15/92 mg group, and all the women discontinued the drug when they learned of the pregnancy. The average gestational age at time of pregnancy diagnosis was 5.4 weeks (MHT Review, pg. 15). No anomalies were noted among the 34 pregnancies.

Eighteen women delivered normal healthy infants; 3 women had spontaneous abortions; 10 women had elective terminations; 1 woman had an ectopic pregnancy; and 1 pregnancy was ongoing at the time of NDA submission; however, the fetus has been diagnosed with Down’s syndrome via pre-natal testing, including amniocentesis (MHT Review, pg. 15).

**Reviewer Comment:** The MHT review stated that Down’s syndrome is a chromosomal disorder caused by an error in cell division that results in the presence of an additional third chromosome 21. The National Institute of Child Health and Development (www.nichd.nih.gov) reports that Down’s Syndrome is a random event and occurs in one out of 800 live births in all races and economic groups, and incidence increases with increasing maternal age. There is no evidence that it is due to parental behavior (other than age) or environmental factors.

7. LITERATURE PUBLICATIONS

A number of publications in the medical literature have examined the occurrence of major malformations following prenatal exposure to topiramate. The largest studies doing so are summarized below.

7.1 UK Pregnancy Registry Publication

**Hunt S et al. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register.** Neurology 2008; 71:272-276. The investigators in Hunt et al. examined the outcomes of pregnancies exposed to topiramate within a prospective, observational study. Participants were women with epilepsy who become pregnant while

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taking topiramate either singly or with other antiepileptic drugs (AEDs), and who were referred before outcome of the pregnancy was known. The main outcome of the study was major congenital malformation (MCM) rate. Secondary outcomes were risk of specific MCM, minor malformation rate, birth weight, and gestational age at delivery.

Full outcome data was obtained for 203 pregnancies. Of these, 178 resulted in live birth; 16 had an MCM (9.0%; 95% CI 5.6% to 14.1%). Three MCMs were observed in 70 monotherapy exposures (4.8%; 95% CI 1.7% to 13.3%) and 13 MCMs in pregnancies exposed to topiramate as part of a polytherapy regimen (11.2%; 95% CI 6.7% to 18.2%). Four of the MCMs were oral clefts (2.2%; 95% CI 0.9% to 5.6%). Four cases of hypospadias were reported (5.1%; 95% CI 0.2% to 10.1%) among 78 live male births of which two were classified as major malformations. The investigators concluded that the number of outcomes of human pregnancies exposed to topiramate is low, but the major congenital malformation rate for topiramate polytherapy raises some concerns. The investigators calculated that the rate of oral clefts observed was 11 times the rate in the background population. For the risk of oral clefts in the background population, the authors referenced to “Harper PS. Practical Genetic Counseling, 6th ed. Arnold; 2004.”

**Reviewer comment:** Limitations of this study include a relatively small number of malformations, wide confidence intervals, and lack of concurrent control group. However, this pregnancy registry study does replicate the finding of an elevated relative risk for oral clefts following topiramate exposure.

### 7.2 NAAED Pregnancy Registry Publication

**Hernandez-Diaz S, Mittendorf R, Holmes LB. Abstract: Comparative Safety of Topiramate during Pregnancy (Teratology Society Program 2010, W9, pg. 408).** The investigators referenced the study by Hunt et al. (above) as a prior publication on the subject. Using data from the NAAED pregnancy registry, the investigators compared the frequency of adverse pregnancy outcomes in women treated with topiramate monotherapy to the frequency in the control group (friends and family of the study group who were not exposed to AEDs). The prevalence of major malformations in women exposed to topiramate during the first trimester was 3.8% (11/289) and 1.3% (5/372) in the unexposed reference group. The relative risk for topiramate was therefore 2.8 (95% C.I. 1.0 – 8.1).

Four infants exposed to topiramate had cleft lip: two (0.69%) of which were isolated. The investigators stated that the expected prevalence of isolated cleft lip (in the general population) is 0.07%. The prevalence of low birth weight (<2,500 grams) in live born singletons without major malformations was 9.8% for topiramate and 3.6% for controls (RR 2.7, 95% C.I. 1.4 – 5.1). Prenatal exposure to topiramate was associated with a mean decrease in birth weight of 307 grams (placebo 0.001) compared to controls. For lamotrigine and carbamazepine, the mean decrease in birth weights were 74 and 94 grams, respectively, which was not statistically significant.

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7 See Attachment 10.2 for details on the NAAED registry protocol.
This data was presented as an abstract at the 2010 meeting of the Teratology Society Program.

7.3 Teratogen Information Service Publication

Ornoy A, Naama Z, Arnon J et al. The outcome of pregnancy following topiramate treatment: a study of 42 cases. Reproductive Toxicology 2008: 388-389. The investigators asserted that their study was prompted by “a substantial increase in the use of topiramate at child bearing age.”

Reviewer comment: The publication did not elaborate on their assertion that use of topiramate during pregnancy was increasing.

The authors followed the outcome of pregnancies of women who contacted the Israeli Teratogen Information Service (TIS) between January 1996 and December 2006 in regard to exposure to topiramate. The outcome of 52 pregnancies (29 monotherapy, 23 polytherapy) with 11 abortions and 41 liveborn infants was compared to the outcome of 212 pregnancies with 198 liveborn infants of women who contacted our TIS at the same period of time and were exposed to non-teratogenic agents.

As with the NAAED pregnancy registry, there were baseline differences in the topiramate-treated mothers compared to the mothers in the control group. Specifically, women treated with topiramate had initial contact with the registry earlier (average 7 weeks) compared to controls. In addition, spontaneous abortions (11.3%) were significantly higher in topiramate-treated mothers in comparison to controls (2.8%).

The authors concluded that topiramate reduces birth weight without decreasing gestational age at delivery, but did not increase the risk for structural defects. The sponsors also stated that “There was an increased rate of spontaneous abortions not related to the drug effects.”

Reviewer comment: This is the second pregnancy registry which found a decreased birth weight, suggesting that this is a valid safety signal. This registry did not find an increased risk of oral clefts. However, this registry collected data from only 29 pregnancies exposed to topiramate monotherapy, compared to 289 in the NAAED registry and 70 in the UK registry.

8. CONCLUSIONS AND RECOMMENDATIONS

8.1 Overview

The Division examined three issues with regard to the teratogenicity of topiramate: oral clefts, low birth weight and hypospadias. The Division concluded that due to the reasons outlined in Section 8.2 of this review, the relationship between prenatal topiramate exposure and oral clefts should be considered a causal and described in the labeling. The Division believed that there was insufficient evidence at present to describe the adverse
events of low birth weight and hypospadias in labeling. However, the Division believes that that these issues (low birth weight and hypospadias) deserve close monitoring as additional data accrue.

To better inform patients and prescribers of the increased risk of oral clefts with prenatal topiramate exposure, the Division collaborated with the sponsor and other divisions of the FDA to prepare a Drug Safety Communication (DSC) regarding the risk of oral clefts. This DSC is scheduled to be made public in March 2011. In addition, a DHCP provider letter will also be issued.

8.2 Oral Clefts

This review examines multiple data sources related to the teratogenicity of topiramate. These sources include preclinical studies, reports from the North American AED (NAAED) registry, publications of data from other registries and an AERS case series with datamining. A number of factors suggest a causal relationship between prenatal topiramate exposure and subsequent major congenital malformations, specifically oral clefts. These factors are described below.

1. **Biological Plausibility:** In mouse studies, doses that are 20% of the human dose produced malformations, mainly of the craniofacial complex. In rats, doses which are 20% of the human dose reduced fetal bodyweight and higher doses produced various craniofacial and limb anomalies. The fact that craniofacial malformations, specifically oral clefts, occur in both preclinical and clinical studies supports the biological plausibility of a causal relationship to oral clefts.

2. **Reproduction of Findings:** Two separate pregnancy registries, the NAAED and another based in the UK, found an elevated risk of oral clefts in women treated with topiramate compared to various control groups. This elevation included a relative risk of 21 in the NAAED registry\(^8\) and 11 in the UK registry. In addition, a search of the AERS database found 11 cases of oral clefts among 64 total reports of prenatal topiramate exposure. AERS datamining found an EB 05 of 36 for cleft lip and palate in topiramate reports, which is an outlier compared to reports from other AEDs.

3. **Strength of Effect:** Although some drug effects produce a small but true increase in relative risk, larger effects are less likely to be a chance occurrence than smaller effects. For prenatal topiramate exposure and oral clefts, the effect is relatively substantial. As noted above, the relative risk was 21 for data from the NAAED registry and 11 in a registry based in the UK.

Factors that are not supportive of a causal association between prenatal topiramate exposure and major congenital malformations include the fact that a third pregnancy registry study (Ornoy et. al) did not find an increase in oral clefts when compared to controls. However, this registry collected data from only 29 pregnancies exposed to topiramate.

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\(^8\) This comparison with the Relative Risk of 21 was between topiramate exposed infants and infants born to the background population of women delivering at the same hospital at which the registry is based.
topiramate monotherapy, compared to 289 in the NAAED registry and 70 in the UK registry. A limitation of the pregnancy registry studies (NAAED, Teratogen Information Service and UK registries) was that topiramate-treated mothers differed at baseline from mothers in the control groups. Some of these differences were substantial, and involved factors that are significant in pregnancy, such as education level, alcohol intake and smoking.

Based on the evidence outlined in this review, the Division concluded that prenatal exposure to topiramate is causally associated with an increase in the risk of oral clefts.

8.3 Decreased Birth Weight

In addition to oral clefts, another pregnancy complication that was observed repeatedly across data sources was decreased birth weight. As with oral clefts, decreased birth weight was seen in preclinical studies. Both the NAAED registry (in the annual reports) and the UK registry (in the literature publication by Hunt et al.) found a decrease in birth weight, as did the Teratogen Information Service study (Ornoy et al). In addition, as with the signal for oral clefts, the signal for decreased birth weight was fairly strong. In the NAAED registry, the prevalence of low birth weight (<2,500 grams) in live born singletons without major malformations was 9.8% for topiramate and 3.6% for controls (RR 2.7, 95% CI 1.4 – 5.1). An elevated risk for low birth weight RR 1.75; 95% CI 1.13 to 2.76; p = 0.013) compared to other infants exposed to AEDs was also observed in the NAAED registry data. Finally, the occurrence of decreased birth weight is biologically plausible based on metabolic acidosis. The current topiramate pregnancy labeling notes that “The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) may be associated with decreased fetal growth.”

A major limitation of the low birth weight analysis was that in the NAAED registry the mothers treated with topiramate differed from mothers treated with other AEDs in several important factors that could influence birth weight, such as a greater level of smoking and alcohol intake, as well as a lower education level.

8.4 Hypospadias

In their initially proposed language, the sponsor had mentioned cases of hypospadias occurring following topiramate exposure. In addition, some of the literature reports reviewed with regard to oral cleft data also described cases of hypospadias. The Division considered the following data in their review of hypospadias following prenatal topiramate exposure:

- In the Hunt et al. UK Register study, “Four cases of hypospadias were reported (5.1%; 95% CI0.2% to 10.1%) among 78 known live male births of which two were classified as major malformations.” However, there were only three MCMs (including 2 cases of hypospadias) in the 70 monotherapy exposures (of which only 62 resulted in a live birth). If you limit the calculation to just the one hypospadias
MCM (excluding the two minor ones) and monotherapy live births, (1/62) the risk of hypospadias was only 1.6%, approximately five times the background rate cited in the publication.

FDA Table 14: Major Congenital Malformations following Topiramate Monotherapy in the UK Pregnancy Registry Study (Table 2 from Hunt et al. publication)

<table>
<thead>
<tr>
<th>No.</th>
<th>Dose TPM during pregnancy/d, mg</th>
<th>Maternal age, y</th>
<th>Parity</th>
<th>Seizure type</th>
<th>GTC seizure in pregnancy</th>
<th>Gestational age, wk</th>
<th>Weight, g</th>
<th>Sex</th>
<th>Major congenital malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>29</td>
<td>G3P2</td>
<td>Partial</td>
<td>NR</td>
<td>41</td>
<td>3,850</td>
<td>F</td>
<td>Cleft lip and bilateral cleft palate</td>
</tr>
<tr>
<td>2</td>
<td>400</td>
<td>34</td>
<td>G3P2</td>
<td>NR</td>
<td>No</td>
<td>37</td>
<td>2,355</td>
<td>M</td>
<td>Hypospadias</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
<td>27</td>
<td>G1P1</td>
<td>NR</td>
<td>Yes</td>
<td>39</td>
<td>3,289</td>
<td>NR</td>
<td>Cleft lip and palate</td>
</tr>
</tbody>
</table>

TPM = topiramate; GTC = generalized tonic-clonic seizure; NR = not recorded.

- The UK register used the background statistic that hypospadias occurs in 1 in 300 (0.3%) live births (based on a literature publication for the UK).
- The NAAED investigators stated that it was “unfortunate” that the severity of the hypospadias was not specified in the Hunt et al, UK publication, adding that most affected infant boys have a mild glandular type of hypospadias, which the investigators noted is excluded as a minor anomaly with “no surgical, medical or cosmetic importance” within the NAAED registry (However, the Hunt UK article did note that they classified two cases as a MCM, and two of the four as minor).
- There were two hypospadias cases in topiramate patients in the 2009 NAAED registry report, for a risk of 0.75% (2/265). This is higher than the background risk used in the UK register study (0.3%). However, the 0.3% background risk was derived from a UK, not a North American, population and the risk in the NAAED registry was based on two cases.
- For datamining within the AERS database, the EB05 was 17 for topiramate and hypospadias, compared to 36 for oral clefts. The Division noted, however, that the AERS datamining analysis includes all case reports, not just monotherapy case reports.

**Reviewer comment:** Following review of the data above, the Division concluded that although there was insufficient data at present for inclusion in labeling, the issue should continue to be followed closely.

8.5 Pregnancy Category

The current topiramate pregnancy labeling describes the preclinical findings and states that human data is not available. These circumstances are consistent with Pregnancy Category C (see Attachment 9.3 for details) and topiramate is currently categorized as such. However, given the human data which is now available and described in this
review, the issue of pregnancy category should re-visited. As per the category
descriptions, for the epilepsy indication, Pregnancy Category D is more appropriate:

**Pregnancy Category D:** There is positive evidence of fetal risk based on adverse
reaction data from investigational or marketing experience or studies in humans,
BUT the potential benefits from the use of the drug in pregnancy women may be
acceptable despite its potential risks (for example, if the drug is needed in a life-
threatening situation or serious disease for which safer drugs cannot be used or
are ineffective).

### 8.6 Labeling Recommendations

The Division, following review of the sponsor’s submissions and proposed labeling, has
updated the topiramate labeling to reflect the emerging signal regarding oral clefts and
prenatal topiramate exposure. The updated labeling is contained in its entirety in Section
9.4 of this review.

### 8.7 FDA Drug Safety Communication and DHCP Letter

The Division believed that the occurrence of oral clefts following prenatal topiramate
exposure represented a sufficient safety signal that it should be more widely
communicated to patients and prescribers through use of an FDA Drug Safety
communication. This communication is planned for release in March 2011, and
describes the oral cleft data from the NAAED registry.
9. ATTACHMENTS

9.1 Topiramate Pregnancy-Related Labeling

8.1 Pregnancy

Pregnancy Category C.

Topiramate may cause serious adverse fetal effects, based on clinical and nonclinical data. Topiramate treatment is associated with 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) may be associated with 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.
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.

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/m² 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/m² 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/m² 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/m² basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m² 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/m² basis) and reductions in preand/ or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m² 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/m² basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m² basis) and higher.

Pregnancy Registry
The North American Drug Pregnancy Registry has been established to collect information and provide scientific knowledge about safety and outcomes associated with pregnant women being treated with antiepileptic drugs. It is desirable that the experience from patients who are exposed to topiramate during pregnancy be reported to this registry. Such information can be reported to the North American Drug Pregnancy Registry by either a healthcare provider or the patient by calling 1-888-233-2334. Information about the North American Drug Pregnancy Registry can be found at http://www.massgeneral.org/aed/.

8.2 Labor and Delivery

Although the effect of TOPAMAX® on labor and delivery in humans has not been established, the development of topiramate-induced metabolic acidosis in the mother and/or in the fetus might affect the fetus’ ability to tolerate labor [see Pregnancy (8.1)].

8.3 Nursing Mothers

Limited data on 5 breastfeeding infants exposed to topiramate showed infant plasma topiramate levels equal to 10-20% of the maternal plasma level. The effects of this exposure on infants are unknown. Caution should be exercised when administered to a nursing woman.

9.2 NAAED Pregnancy Registry Methodology

The North American AED Pregnancy Registry was established at the Massachusetts General Hospital in Boston in December, 1996. The current sponsors of the Registry are these six companies: Abbott, Eisai, Novartis, Ortho-McNeil, Pfizer and Sepracor. In addition, there are five companies which are Contributors to the Registry: Aurobindo Pharma, Dr. Reddy’s Laboratories, GlaxoSmithKline, Sandoz and Teva Pharmaceuticals.

The discussions of the findings for each drug have occurred in a private meeting with the members of the Scientific Advisory Committee at the semi-annual meetings. After those separate meetings, the Scientific Advisory Committee reviews their decisions about releasing findings with the representatives of each sponsoring company, the Steering Committee of the Registry.

A. Methodology:

The goal of the Registry is to determine, from the outcomes of the pregnancies of each enrolled woman, the health status of her infant, with a particular focus on the occurrence of major malformations. There are several steps:

1. the woman calls the toll-free number (1-888-233-2334) to ask about the study; if she decides to enroll, her informed consent is obtained verbally;
2. she is asked a series of questions by the Research Assistant to determine the medication she is taking, information about her epilepsy (or any other condition for which she is taking an anticonvulsant drug), other exposures (alcohol, smoking, etc.) and demographic characteristics;

3. the second interview is at 7 months gestation and is used to confirm her address and telephone number (about 10% have changed), to record changes in her medication and to ask if any fetal abnormalities have been identified by prenatal testing;

4. the third interview is conducted at 8 to 12 weeks after the woman’s expected date of delivery; the mother is asked about the health status of her infant; with her written permission, information is obtained about the findings in her infant by her infant’s pediatrician or family practitioner and about her health status with reports from her neurologist or psychiatrist;

5. the responses in each interview and the findings in all medical reports on the infants exposed to each drug as monotherapy or polytherapy are tabulated and analyzed.

B. Inclusion/exclusion criteria:

The definition used for a major malformation is a structural abnormality with surgical, medical or cosmetic importance. The findings in the examination are reviewed by Holmes (teratologist), blinded to exposure status, to determine whether the abnormality is “included or excluded.” A decision tree is maintained to insure consistency in the handling of the same finding in more than one infant.

The features excluded as not being a major malformation are:

1. minor anomalies (transverse palmar crease);
2. birth marks (hemangiomas);
3. positional deformations (hip dislocation in a breech presentation);
4. a complication of prematurity, defined as birth before 37 weeks gestation (undescended testes, patent ductus arteriosus);
5. chromosome abnormalities (Down Syndrome);
6. genetic disorder (achondroplasia, Holt-Oram Syndrome);
7. a finding in prenatal ultrasound that is not found by examining pediatrician (unilateral renal agenesis);
8. biochemical abnormality (hemoglobin abnormality or cystic fibrosis) identified in newborn screening;
9. finding by echocardiogram with no physiologic significance (tiny atrial septal defect; less than 0.4 cm diameter).

10. any functional deficit, such as failing the newborn screening test for hearing.

The analysis of the findings in phenobarbital-exposed and valproate-exposed pregnancies, released by the Registry in 2004 (1) and 2005 (2) respectively, showed that 17% of the infants had a physical feature that was excluded, as not being a major malformation. By comparison, the rates of major malformations in these two groups of infants were 6.5% and 10.7% respectively. The higher frequency of the features excluded emphasizes the importance in a pregnancy registry of having detailed inclusion and exclusion criteria. The articles and abstracts published from the findings in the Registry are listed in the Appendix.

C. Comparison populations:
Two comparison populations are used: 1) an external comparison group, the newborn infants surveyed for malformations at Brigham and Women’s Hospital (BWH) in Boston; 2) an internal control group recruited by the Registry among the friends and family members of the enrolled women.

1. Newborn infants at BWH: The Active Malformations Surveillance Program at BWH, directed by L.B. Holmes, began in 1972 and has continued to the present time. The same inclusion and exclusion criteria, described above and used by the Registry, are used in the Surveillance Program. All malformed infants are identified by the Research Assistants in a review (six days a week) of the medical charts of each newborn infant. Stillborn infants and elective terminations for fetal anomalies are included. The apparent etiologies of all malformations in the first ten years among 69,277 infants, stillbirths and elective terminations were described by K. Nelson and L.B. Holmes in an article in the New England J Medicine 320:19-23, 1989 (3). The prevalence rate of all malformations was 2.24%. After excluding chromosome abnormalities and genetic disorders, the rate was 1.62%. A review of the prevalence rate of major malformations identified in the years 1974, 1979, 1984, 1989, 1994 and 1999 showed that the prevalence rate had remained very similar over these years (4). The 206,224 infants and elective terminations surveyed in the years 1972-1974, 1979-2000 have been the basis for the prevalence rates of specific malformations, such as isolated cleft lip and/or palate, used in the analysis of those specific outcomes in the release of the findings in lamotrigine-exposed infants (5).

2. Internal controls: The North American AED Pregnancy Registry began to enroll unexposed control mothers and their infants in 2003. These controls have been recruited through the “Friends and Family” of enrolled women. By January 1, 2010, 389 women had enrolled. A comparison of the first 184 women who enrolled as controls showed that their demographic characteristics were very similar to those of the 124 enrolled anticonvulsant-taking women who had recruited them. The experience with recruiting controls was presented at the 2008 annual meeting of the Teratology Society and published in the annual meeting issue of Birth Defects Research (Part A): Clinical Molecular Teratology (6).
D. Guidelines for data analysis and publication for the North American AED Pregnancy Registry:
The Scientific Advisory Committee developed and approved the following guidelines at its meeting on June 5, 2002:

1. Two groups of eligible women will be enrolled: the “pure” prospective enrollees, who have had no prenatal screening, and the “traditional” prospective enrollees, who have had this screening.

The findings in infants born to “traditional” prospective enrollees can be combined with the “pure” prospective enrollees in the analysis of the findings.

2. The primary outcome to be studied will be major malformations. The inclusion and exclusion criteria for major malformations are the same as have been used in the external comparison group, the Active Malformations Surveillance Program at BWH and the internal comparison group recruited by the Registry staff.

3. Publication of results for a positive association (RR>1) would occur when the lower confidence limit is 2.0 or higher. In this way, we would be 95% confident that there is at least a two-fold increase. The first two publications of positive associations were for the drugs phenobarbital (1) and sodium valproate (2), used as monotherapy.
4. Publication of results for drugs with no association would occur when the upper confidence limit does not exceed 2.0. This would allow us to say with 95% confidence that the increase in risk was not greater than 100%.

E. Revision of release criteria:

The Scientific Advisory Committee and the Registry Staff found that the release criteria developed initially were not adequate for commonly used drugs, such as lamotrigine and carbamazepine, which were not associated with a significant increase in the frequency of all major malformations. After enrolling 500 to 700 eligible women exposed to each of these drugs, the Scientific Advisory Committee explored new criteria to use to evaluate the associated outcomes.

In June and August, 2005, the Scientific Advisory Committee decided to release the findings in lamotrigine (LTG)-exposed pregnancies, using the “Rule of Three” as the basis (7). At the time this decision was made, there were 564 analyzable births. The proportion of major anomalies was 15/564 = 2.7% (95% CI: 1.5-4.3%). (This finding did not meet the release criteria for all malformations, as the lower 95 CI was not above 2.)

These criteria for the release of findings for specific malformations will be followed whenever three or more infants have the same common malformation among 500 to 700 infants exposed to the same anticonvulsant drug as monotherapy.

F. Development of Annual Reports:

At the semi-annual meeting with the Scientific Advisory Committee and the Steering Committee in December, 2007, it was announced that beginning in 2009, an annual report format would be developed for each monotherapy. These reports would be limited to those drugs for which there were at least 50 exposed infants.

This is the annual report on infants born after 6,685 exposed pregnancies, whose mothers enrolled in the Registry with estimated date of delivery was January 1, 2010 or earlier and reported having taken oxcarbazepine during that pregnancy.

**Contributors:** This new category of support for the Registry was proposed in 2008 and is being implemented in 2009. The Contributors will receive Adverse Event Reports concerning malformations, spontaneous abortions or stillbirths in infants of enrolled women who took their product as monotherapy. The Contributor will receive, each year, a list of the malformations reported and the total number of enrolled pregnancies. When 50 eligible, monotherapy-exposed pregnancies have been enrolled and the outcomes determined, an Annual Report will be sent to each Contributor. The Contributors are not listed in the publications of the Registry or at the exhibit presented at the annual meeting of the American Epilepsy Society. Representatives of the Contributors are not invited to the Scientific Advisory Committee.

References:

5. The enrolling woman is told in the interviews that she will be asked to provide her written permission for the Registry to obtain copies of the findings in the examinations of her infant in the first 3 months of life. If seen by a consultant, such as a cardiologist or a urologist, permission is requested to obtain those records, as well. Her medical records (from her neurologist or psychiatrist) are also requested.

**Adverse Event Reports:** When a malformation is reported by the mother and is confirmed, an Adverse Event Report is sent by facsimile from the Registry to the manufacturer, if a Sponsor of the Registry. The outcomes reported in the Adverse Event Reports are: malformations, spontaneous abortions and stillbirths.

**Comparison groups and inclusion/exclusion criteria:** The Registry has two comparison groups, one internal (1) and one external (2, 3). The internal “controls” are friends and family members of enrolled women. Through 2008, 340 had been enrolled. The external controls are infants surveyed at birth in a separate Active Malformations Surveillance Program at Brigham and Women’s Hospital (BWH) in Boston. This external group has been used for comparison in all malformations, as well as the frequency of specific malformations, such as isolated cleft palate in 206,244 births. The Surveillance Program at BWH uses the same inclusion/exclusion criteria as the Registry and is directed by Dr. Holmes, the Director of the Registry.

For inclusion, a malformation must be a structural abnormality with surgical, medical or cosmetic importance. Findings by the examining pediatrician which are excluded are: birth marks, minor anomalies, positional deformities, genetic disorders, chromosome abnormalities, prematurity-related findings, and findings in prenatal ultrasound that were not identified at birth by the examining physician.

**Review and release of findings:** Every six months, the staff selects and presents major findings to the independent Scientific Advisory Committee for review and discussion. The five members of the Committee include neurologists (2), obstetrician-epidemiologist (1), birth defects specialist (1) and epilepsy specialist (1). In addition, consultants in psychiatry and epileptology join some of the meetings. Criteria have been established for the release of
significant increases in all malformations, as well as an increase in specific malformations, such as isolated cleft palate.

**Findings published**: The findings published have included an increased frequency of malformations in phenobarbital monotherapy-exposed pregnancies (4) and in valproate monotherapy-exposed pregnancies (5), as well as an increased frequency of cleft palate in lamotrigine monotherapy-exposed pregnancies (6).

An analysis of the correlation of the type of epilepsy in the mother with the rate of malformations in valproate-exposed pregnancy has also been reported (7).

New findings have been published each year, since 2004, in abstract form and are usually published in a manuscript within two years.

**Sponsors**: There are five sponsors of the Registry in 2009 – 2011: Abbott, Eisai, Novartis, Ortho-McNeil and Pfizer. The Sponsors are invited to meet every six months with the Registry staff and the Scientific Advisory Committee to hear, first-hand, the decisions that had been made at a separate meeting by the staff and the Advisors. Their comments and suggestions of the representatives of each Sponsor are invited. The sponsoring companies are listed in each publication from the Registry and are listed at the exhibit presented each year by the Registry at the annual meeting of the American Epilepsy Society.
## 9.3 FDA Pregnancy Category Definitions

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).</td>
</tr>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).</td>
</tr>
<tr>
<td>C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).</td>
</tr>
</tbody>
</table>
9.4 Updated Topiramate Pregnancy Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TOPAMAX® safely and effectively. See full prescribing information for TOPAMAX®

TOPAMAX (topiramate) TABLETS for oral use
TOPAMAX (topiramate capsules) SPRINKLE CAPSULES for oral use
Initial U.S. Approval – 1996

INDICATIONS AND USAGE
• Monotherapy: Initial monotherapy in patients ≥10 years of age with partial or primary generalized tonic-clonic seizures (1.1)
• Adjunctive therapy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (1.2)
• Migraine: Treatment for adults for prophylaxis of migraine headache (1.3)

DOSE AND ADMINISTRATION
See DOSAGE AND ADMINISTRATION, Epilepsy: Adjunctive Therapy Use for additional details (2.1)

<table>
<thead>
<tr>
<th>Epilepsy monotherapy: adults and pediatric patients</th>
<th>Initial Dose</th>
<th>Titration</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/day in two divided doses</td>
<td></td>
<td></td>
<td>400 mg/day in two divided doses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epilepsy adjunctive therapy: adults with partial onset seizures or LGS</th>
<th>Initial Dose</th>
<th>Titration</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 to 50 mg/day</td>
<td></td>
<td></td>
<td>200-400 mg/day in two divided doses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epilepsy adjunctive therapy: adults with primary generalized tonic-clonic seizures</th>
<th>Initial Dose</th>
<th>Titration</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/day (or less, based on a range of 1 to 3 mg/kg/day nightly for the first week)</td>
<td></td>
<td></td>
<td>400 mg/day in two divided doses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS</th>
<th>Initial Dose</th>
<th>Titration</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/day (or less, based on a range of 1 to 3 mg/kg/day nightly for the first week)</td>
<td></td>
<td></td>
<td>5 to 9 mg/kg/day in two divided doses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Migraine (2.3)</th>
<th>Initial Dose</th>
<th>Titration</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/day administered nightly for the first week</td>
<td></td>
<td></td>
<td>100 mg/day administered in two divided doses</td>
</tr>
</tbody>
</table>

DOSE FORMS AND STRENGTHS
• Tablets: 25 mg, 50 mg, 100 mg, and 200 mg (3)
• Sprinkle Capsules: 13 mg and 25 mg (3)

CONTRAINDICATIONS
None.

WARNINGs AND PRECAUTIONS
• Acute myopia and secondary angle-closure glaucoma: Untreated elevated intraocular pressure can lead to permanent visual loss. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible (5.1)
• Oligohydramnios and hyperthermia: Monitor decreased sweating and increased body temperature, especially in pediatric patients (5.2)
• Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal behavior or ideation (5.3)
• Metabolic acidosis: Baseline and periodic measurement of serum bicarbonate is recommended. Consider dose reduction or discontinuation of TOPAMAX® if clinically appropriate (5.4)
• Cognitive and neuropsychiatric (ADEOS®) may cause cognitive dysfunction. Patients should use caution when operating machinery including automobiles. Depression and mood problems may occur in epilepsy and migraine populations (5.5)
• Fetal Toxicity: TOPAMAX® use during pregnancy can cause cleft lip and/or palate. (5.6)
• Withdrawal of AEDs: Withdrawal of TOPAMAX® should be done gradually (5.7)
• Hypersensitivity and encephalopathy associated with or without concomitant valproic acid use: Patients with unformed errors of metabolism or reduced metabolic activity may have an increased risk of hyperammonemia. Measure ammonia if encephalopathic symptoms occur (5.9)
• Kidney stones: Use with other carbonic anhydrase inhibitors, other drugs causing metabolic acidosis, or in patients on a ketogenic diet should be avoided (5.10)

ADVERSE REACTIONS
The most common (≥5% more frequent than placebo or low dose topiramate in monotherapy) adverse reactions in controlled, clinical trials were paresthesia, anorexia, weight decrease, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, difficulty with memory, difficulty with concentration/intention, and confusion. The most common (≥5% more frequent than placebo) adverse reactions in controlled, migraine clinical trials were paresthesia and taste perversion (6.1)

DRUG INTERACTIONS
Summary of antiepileptic drug (AED) interactions with TOPAMAX® (7.3)

USE IN SPECIFIC POPULATIONS
• Renal Impairment: In renally impaired patients (creatinine clearance less than 70 mL/min 1.73 m³), one half of the adult dose is recommended (2.4)
• Patients Undergoing Hemodialysis: Topiramate is cleared by hemodialysis. Dosage adjustment is necessary to avoid rapid doses in topiramate plasma concentration during hemodialysis (2.6)
• Pregnancy: Increased risk of cleft lip and/or palate. Pregnancy registry available. (8.1)
• Nursing Mothers: Caution should be exercised when administered to a nursing mother (8.3)
• Geriatric Use: Dosage adjustment may be necessary for elderly with impaired renal function (8.4)

Reference ID: 2913276
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 1-888-233-2334. 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 an 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/m² 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/m² 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/m² 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/m² basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m² 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/m² basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m² 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/m² basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m² basis) and higher.

MEDICATION GUIDE

TOPAMAX® (Toe-pa-max)
(topiramate)
Tablets and Sprinkle Capsules
Read this Medication Guide before you start taking TOPAMAX® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about TOPAMAX®, talk to your healthcare provider or pharmacist.

What is the most important information I should know about TOPAMAX®?

- **TOPAMAX® may cause eye problems.** Serious eye problems include:
  - any sudden decrease in vision with or without eye pain and redness,
  - a blockage of fluid in the eye causing increased pressure in the eye (secondary angle closure glaucoma).
  - These eye problems can lead to permanent loss of vision if not treated. You should call your healthcare provider right away if you have any new eye symptoms.

- **TOPAMAX® may cause decreased sweating and increased body temperature (fever).** People, especially children, should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition.

- **Like other antiepileptic drugs, TOPAMAX® may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood
Do not stop TOPAMAX® without first talking to a healthcare provider.

- Stopping TOPAMAX® suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Topamax can harm your unborn baby.

- 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.
- Cleft lip and cleft palate may happen even in children born to women who are not taking any medicines and do not have other risk factors.
- 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. You should talk to your doctor about the best kind of birth control to use while you are taking TOPAMAX®.
- Tell your healthcare provider right away if you become pregnant while taking TOPAMAX®. You and your healthcare provider should decide if you will continue to take TOPAMAX® while you are pregnant.
- Pregnancy Registry: If you become pregnant while taking TOPAMAX®, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The
The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.

What is TOPAMAX®?

TOPAMAX® is a prescription medicine used:

- to treat certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in people 10 years and older,
- with other medicines to treat certain types of seizures (partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 2 years and older,
- to prevent migraine headaches in adults.

What should I tell my healthcare provider before taking TOPAMAX®?

Before taking TOPAMAX®, tell your healthcare provider about all your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior
- have kidney problems, have kidney stones, or are getting kidney dialysis
- have a history of metabolic acidosis (too much acid in the blood)
- have liver problems
- have osteoporosis, soft bones, or decreased bone density
- have lung or breathing problems
- have eye problems, especially glaucoma
- have diarrhea
- have a growth problem
- are on a diet high in fat and low in carbohydrates, which is called a ketogenic diet
- are having surgery
- are pregnant or plan to become pregnant.
- are breastfeeding. TOPAMAX® passes into breast milk. It is not known if the TOPAMAX® that passes into breast milk can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take TOPAMAX®.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. TOPAMAX® and other medicines may affect each other causing side effects.

Especially, tell your healthcare provider if you take:
- Valproic acid (DEPAKENE®, DEPAKOTE®)
- any medicines that impair or decrease your thinking, concentration, or muscle coordination.
- birth control pills. TOPAMAX® may make your birth control pills less effective. Tell your healthcare provider if your menstrual bleeding changes while you are taking birth control pills and TOPAMAX®.

Ask your healthcare provider if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking with your healthcare provider.

How should I take TOPAMAX®?
- Take TOPAMAX® exactly as prescribed.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- TOPAMAX® tablets should be swallowed whole. Do not chew the tablets. They may leave a bitter taste.
- TOPAMAX® sprinkle capsules may be swallowed whole or may be opened and sprinkled on a teaspoon of soft food. Drink fluids right after eating the food and medicine mixture to make sure it is all swallowed.
- Do not store any medicine and food mixture for later use.
- TOPAMAX® can be taken before, during, or after a meal. Drink plenty of fluids during the day. This may help prevent kidney stones while taking TOPAMAX®.
- If you take too much TOPAMAX®, call your healthcare provider or poison control center right away or go to the nearest emergency room.
- If you miss a single dose of TOPAMAX®, take it as soon as you can. However, if you are within 6 hours of taking your next scheduled dose, wait until then to take your usual dose of TOPAMAX®, and skip the missed dose. Do not double your dose. If you have missed more than one dose, you should call your healthcare professional for advice.
- Do not stop taking TOPAMAX® without talking to your healthcare provider. Stopping TOPAMAX® suddenly may cause serious problems. If you have epilepsy
and you stop taking TOPAMAX® suddenly, you may have seizures that do not stop. Your healthcare provider will tell you how to stop taking TOPAMAX® slowly.

- Your healthcare provider may do blood tests while you take TOPAMAX®.

**What should I avoid while taking TOPAMAX®?**

- Do not drink alcohol while taking TOPAMAX®. TOPAMAX® and alcohol can affect each other causing side effects such as sleepiness and dizziness.
- Do not drive a car or operate heavy machinery until you know how TOPAMAX® affects you. TOPAMAX® can slow your thinking and motor skills, and may affect vision.

**What are the possible side effects of TOPAMAX®?**

TOPAMAX® may cause serious side effects including:

See “What is the most important information I should know about TOPAMAX®?”

- **Metabolic Acidosis.** Metabolic acidosis can cause:
  - tiredness
  - loss of appetite
  - irregular heartbeat
  - impaired consciousness

- **High blood ammonia levels.** High ammonia in the blood can affect your mental activities, slow your alertness, make you feel tired, or cause vomiting. This has happened when TOPAMAX® is taken with a medicine called valproic acid (DEPAKENE® and DEPAKOTE®).

- **Kidney stones.** Drink plenty of fluids when taking TOPAMAX® to decrease your chances of getting kidney stones.

- **Effects on Thinking and Alertness.** TOPAMAX® may affect how you think, and cause confusion, problems with concentration, attention, memory, or speech. TOPAMAX® may cause depression or mood problems, tiredness, and sleepiness.

- **Dizziness or Loss of Muscle Coordination.**

Call your healthcare provider right away if you have any of the symptoms above.

The most common side effects of TOPAMAX® include:

- tingling of the arms and legs (paresthesia)
- not feeling hungry
• nausea
• a change in the way foods taste
• diarrhea
• weight loss
• nervousness
• upper respiratory tract infection

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of TOPAMAX®. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Ortho-McNeil Neurologics at 1-800-526-7736.

How should I store TOPAMAX®?

• Store TOPAMAX® tablets at room temperature, 59°F to 86°F (15°C to 30°C).
• Store TOPAMAX® Sprinkle Capsules at or below 25°C (77°F).
• Keep TOPAMAX® in a tightly closed container.
• Keep TOPAMAX® dry and away from moisture.
• Keep TOPAMAX® and all medicines out of the reach of children.

General information about TOPAMAX®.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TOPAMAX® for a condition for which it was not prescribed. Do not give TOPAMAX® to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about TOPAMAX®. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about TOPAMAX® that is written for health professionals.

For more information, go to www.topamax.com or call 1-800-526-7736.
What are the ingredients in TOPAMAX?

Active ingredient: topiramate

Inactive ingredients:

- **Tablets** - lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide and polysorbate 80.

- **Sprinkle Capsules** - sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, sorbitan monolaurate, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

Manufactured by: Janssen Ortho, LLC, Gurabo, Puerto Rico 00778


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This Medication Guide has been approved by the U.S. Food and Drug Administration.

[Insert component code]

Revised February 2011
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARION L JONES
03/03/2011

SALLY U YASUDA
03/03/2011