CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
(PROPOSITION 65)

NOTICE OF INTENT TO LIST TOPIRAMATE
OCTOBER 2, 2015

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intends to list topiramate as known to the state to cause reproductive toxicity (developmental endpoint) under the Safe Drinking Water and Toxic Enforcement Act of 1986[1]. This action is being proposed under the "Formally Required to Be Labeled or Identified" listing mechanism[2].

Chemical	CAS No.	Toxicological Endpoint	Reference
Topiramate	97240-79-4	Developmental toxicity	FDA (2015) FDA (2014 a,b)

Background on listing via the formally required to be labeled or Identified mechanism: A chemical must be listed under Proposition 65[3] and its implementing regulations (Section 25902[4]) when a state or federal agency has formally required it to be labeled or identified as causing cancer or reproductive toxicity.

OEHHA is the lead agency for Proposition 65 implementation, and evaluates whether listing under Proposition 65 is required pursuant to the definitions set out in Section 25902. According to Section 25902(b):

- "'[F]ormally required' means that a mandatory instruction, order, condition, or similar command, has been issued in accordance with established policies and procedures of an agency of the state or federal government to a person or legal entity outside of the agency. The action of such agency may be directed at one or more persons or legal entities and may include formal requirements of general application;"

[1] Commonly known as Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986 is codified in Health and Safety Code section 25249.5 *et seq*.
[2] See Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25902.
[3] See Health and Safety Code section 25249.8(b).
[4] All referenced regulatory sections are from Title 27 of the Cal. Code of Regulations.

- "'[L]abeled' means that a warning message about the carcinogenicity or reproductive toxicity of a chemical is printed, stamped, written, or in any other manner placed upon the container in which the chemical is present or its outer or inner packaging including any material inserted with, attached to, or otherwise accompanying such a chemical;"
- "'[I]dentified' means that a required message about the carcinogenicity or reproductive toxicity of the chemical is to be disclosed in any manner to a person or legal entity other than the person or legal entity who is required to make such disclosure"; and
- "As causing reproductive toxicity" means: "For chemicals that cause reproductive toxicity, the required label or identification uses any words or phrases intended to communicate a risk of reproductive harm to men or women or both, or a risk of birth defects or other developmental harm."

OEHHA's determination: *Topiramate* has been identified and labeled to communicate a risk of reproductive harm (developmental toxicity endpoint) (FDA, 2015; 2014a; b) in accordance with formal requirements by the US Food and Drug Administration (FDA). The FDA-approved labels indicate that uses of *topiramate* during pregnancy can cause cleft lip and/or palate. Topamax, QUDEXY XR, and QSYMIA are trade names of drugs that are composed of or include topiramate.

Language from FDA-approved product labels which meets the requirements of Section 25902 is quoted below:

Topiramate

Reproductive Toxicity (Developmental Endpoint)

1. FDA-approved label Reference ID 3723186 (FDA, 2015)

Under HIGHLIGHTS OF PRESCRIBING INFORMATION. WARNINGS AND PRECAUTIONS:
"Fetal toxicity: Topiramate use during pregnancy can cause cleft lip and/or palate (5.7)".

Under WARNINGS AND PRECAUTIONS:
"**5.7 Fetal Toxicity**. Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural

malformations, including craniofacial defects, and reduced fetal weights occurred in offspring *[see Use in Specific Populations (8.1)]*".

"Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus *[see Use in Specific Populations (8.1 and 8.9)]*".

Under USE IN SPECIFIC POPULATIONS**:**
"8.1 Pregnancy. Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring. Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus *[see Use in Specific Populations (8.9)]*".

*"***8.9 Women of Childbearing Potential.** Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts) *[see Warnings and Precautions (5.7) and Use in Specific Populations (8/1)]*. Consider the benefits and risks of topiramate when prescribing this drug to women of childbearing potential, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. Because of the risk of oral clefts to the fetus, which occur in the first trimester of pregnancy before many women know they are pregnant, all women of childbearing potential should be apprised of the potential hazard to the fetus from exposure to topiramate."

2. FDA-approved label Reference ID 3675672 (FDA, 2014a).

Under HIGHLIGHTS OF PRESCRIBING INFORMATION. WARNINGS AND PRECAUTIONS:
"Fetal Toxicity: TOPAMAX® [topiramate] use during pregnancy can cause cleft lip and/or palate (5.7).".

Under WARNINGS AND PRECAUTIONS:
"**5.7 Fetal Toxicity**. TOPAMAX® [topiramate] can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk of cleft lip and/or cleft palate (oral clefts).

When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring *[see Use in Specific Populations (8.1)].*"

"TOPAMAX® [topiramate] should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1) and (8.9)]*".

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

"Human Data. "Data from the NAAED [North American Antiepileptic Drug] Pregnancy Registry (425 prospective topiramate monotherapy-exposed pregnancies) indicate an increased risk of oral clefts in infants exposed during the first trimester of pregnancy. The prevalence of oral clefts among topiramate-exposed infants was 1.2% compared to a prevalence of 0.39% for infants exposed to a reference AED. In infants of mothers without epilepsy or treatment with other AEDs, the prevalence was 0.12%. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a similar background rate of 0.17%." "The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval [CI] 4.0 – 23.0) as compared to the risk in a background population of untreated women."

*"***8.9 Women of Childbearing Potential.** Data from pregnancy registries indicate that infants exposed to TOPAMAX® [topiramate] *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts) *[see Warnings and Precautions (5.7) and Use in Specific Populations (8/1)]*. Consider the benefits and risks of TOPAMAX® when prescribing this drug to women of childbearing potential, particularly when TOPAMAX® is considered for a condition not usually associated with permanent injury or death. Because of the risk of oral clefts to the fetus, which occur in the first trimester of pregnancy before many women know they are pregnant, all women of childbearing

potential should be apprised of the potential hazard to the fetus from exposure to TOPAMAX®."

3. FDA-approved label Reference ID 3634966 (FDA, 2014b)

Under HIGHLIGHTS OF PRESCRIBING INFORMATION. WARNINGS AND PRECAUTIONS:
"Fetal Toxicity: Females of reproductive potential: Obtain negative pregnancy test before treatment and monthly thereafter; use effective contraception. Qsymia is available through a limited program under a Risk Evaluation and Mitigation Strategy (REMS) (5.1)."

Under WARNINGS AND PRECAUTIONS**:**
"5.1 Fetal Toxicity. Qsymia can cause fetal harm. Data from pregnancy registries and epidemiology studies indicate that a fetus exposed to topiramate, a component of Qsymia, in the first trimester of pregnancy has an increased risk of oral clefts (cleft lip with or without cleft palate). If Qsymia is used during pregnancy or if a patient becomes pregnant while taking Qsymia, treatment should be discontinued immediately, and the patient should be apprised of the potential hazard to a fetus. Females of reproductive potential should have a negative pregnancy test before starting Qsymia and monthly thereafter during Qsymia therapy. Females of reproductive potential should use effective contraception during Qsymia therapy *[see Use in Specific Populations (8.1) and (8.6)]*."

Under USE IN SPECIFIC POPULATIONS:
"**8.1 Pregnancy**. Risk Summary. Qsymia is contraindicated in pregnant women. The use of Qsymia can cause fetal harm …. Available epidemiologic data indicate an increased risk in oral clefts (cleft lip with or without cleft palate) with first trimester exposure to topiramate, a component of Qsymia. When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring.

If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, treatment should be discontinued immediately and the patient should be apprised of the potential hazard to a fetus".

*"***8.6 Females of Reproductive Potential.** Qsymia can cause fetal harm. Data from pregnancy registries and epidemiology studies indicate that a fetus exposed to

topiramate, a component of Qsymia, in the first trimester of pregnancy has an increased risk of oral clefts (cleft lip with or without cleft palate)."

Request for comments: OEHHA is requesting comments as to whether this chemical meets the criteria set forth in the Proposition 65 regulations for listings via the formally required to be labeled or identified mechanism (Section 25902). Because this is a ministerial listing, comments should be limited to whether FDA requires that *topiramate* be labeled to communicate a risk of reproductive or developmental harm. OEHHA cannot consider scientific arguments concerning the weight or quality of the evidence considered by FDA when it established the labeling requirement and will not respond to such comments if they are submitted.

In order to be considered, **OEHHA must receive comments by 5:00 p.m. on Monday, November 2, 2015.** We encourage you to submit comments in electronic form, rather than in paper form. Comments transmitted by e-mail should be addressed to P65Public.Comments@oehha.ca.gov. Please include "topiramate" in the subject line. Comments submitted in paper form may be mailed, faxed, or delivered in person to the address below.

Mailing Address: Michelle Robinson
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010
Fax: (916) 323-2265
Street Address: 1001 I Street
Sacramento, California 95814

Comments received during the public comment period will be posted on the OEHHA web site after the close of the comment period.

If you have any questions, please contact Michelle Robinson at Michelle.Robinson@oehha.ca.gov or at (916) 445-6900.

References

Food and Drug Administration (FDA, 2015). FDA approved drug label for QUDEXY XR (topiramate), Reference ID 3723186, approved 3-30-2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205122s001lbl.pdf

Food and Drug Administration (FDA, 2014a). FDA approved drug label for TOPAMAX (topiramate), Reference ID 3675672, approved 12-18-2014. Available at

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020505s055,020844s046lbl.pdf

Food and Drug Administration (FDA, 2014b). FDA approved drug label for QSYMIA (contains topiramate), Reference ID, 3634966, approved 9-26-2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022580s010s011s012lbl.pdf