**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 PERTUZUMAB

**September 30, 2016**
**Reissued December 2, 2016**

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intends to list pertuzumab 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 |
|---|---|---|---|
| Pertuzumab | 380610-27-5 | Developmental toxicity | FDA (2015) |

**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:** *Pertuzumab* is a drug used to treat certain types of cancer. It has been identified and labeled to communicate a risk of reproductive harm (developmental endpoint) (FDA, 2015) in accordance with formal requirements by the US Food and Drug Administration (FDA). The FDA-approved label indicates that uses of *pertuzumab* during pregnancy can cause embryo-fetal death and birth defects. PERJETA® is a trade name of the drug pertuzumab.

Language from the FDA-approved product label (Reference ID 3769469; FDA, 2015) which meets the requirements of Section 25902 is quoted below:

***Pertuzumab***

**Reproductive Toxicity (Developmental Endpoint)**

Under HIGHLIGHTS OF PRESCRIBING INFORMATION:
**"WARNING: … EMBRYO-FETAL TOXICITY.** "Embryo-fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. … (5.2, 8.1, 8.6)"

Under FULL PRESCRIBING INFORMATION:
**"WARNING: … EMBRYO-FETAL TOXICITY.** "Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. … (5.2, 8.1, 8.6)"

Under WARNINGS AND PRECAUTIONS:

"**5.2 Embryo-Fetal Toxicity.** PERJETA can cause fetal harm when administered to a pregnant woman. Treatment of pregnant cynomolgus monkeys with pertuzumab resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death. If PERJETA is administered during pregnancy, or if the patient becomes pregnant while receiving this drug or within 7 months following the last dose of PERJETA in combination with trastuzumab, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]."*

"Verify pregnancy status prior to the initiation of PERJETA. Advise patients of the risks of embryo-fetal death and birth defects and the need for contraception during and after treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant."

*Under* USE IN SPECIFIC POPULATIONS**:**

**"8.1 Pregnancy. *Pregnancy Category D.***

Risk Summary

There are no adequate and well-controlled studies of PERJETA in pregnant women. Based on findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. The effects of PERJETA are likely to be present during all trimesters of pregnancy. Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on $C_{max}$. If PERJETA is administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA or within 7 months following the last dose of PERJETA in combination with trastuzumab, the patient should be apprised of the potential hazard to the fetus."

"Animal Data

Reproductive toxicology studies have been conducted in cynomolgus monkeys. Pregnant monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on $C_{max}$. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on $C_{max}$). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights, and microscopic

evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100."

**"8.6 Females of Reproductive Potential.** PERJETA can cause embryo-fetal harm when administered during pregnancy. Counsel patients regarding pregnancy prevention and planning. Advise females of reproductive potential to use effective contraception while receiving PERJETA and for 7 months following the last dose of PERJETA in combination with trastuzumab."

Under PATIENT COUNSELING INFORMATION:
"Advise pregnant women and females of reproductive potential that PERJETA exposure can result in fetal harm, including embryo-fetal death or birth defects *[see Warnings and Precautions (5.2) and Use in Specific │Populations (8.1)]* "

"Advise females of reproductive potential to use effective contraception while receiving PERJETA and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Warnings and Precautions (5.2) and Use in Special Populations (8.6)]* "

**Request for comments:** This notice was previously published in the September 30, 2016 issue of the California Regulatory Notice Register (Register 2016, No. 40-Z). However, it was inadvertently not posted on the OEHHA website at that time and OEHHA is again 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 *pertuzumab* be labeled to communicate a risk of 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 Tuesday, January 3, 2017.** 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 "pertuzumab" in the subject line. Comments submitted in paper form may be mailed, faxed, or delivered in person to the address below.

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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 Ramirez at Michelle.Ramirez@oehha.ca.gov or at (916) 445-6900.

**References**

Food and Drug Administration (FDA, 2015). FDA approved drug label for PERJETA® (pertuzumab), Reference ID 3769469, approved May-2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125409s105lbl.pdf