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 VISMODEGIB

September 30, 2016
Reissued December 2, 2016

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intends to list vismodegib as known to the state to cause reproductive toxicity (developmental, female, and male endpoints) 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
Vismodegib	879085-55-9	Developmental toxicity Female reproductive toxicity Male reproductive 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

[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.

or more persons or legal entities and may include formal requirements of general application;"

- "'[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: *Vismodegib* is a drug used to treat certain types of skin cancer. It has been identified and labeled to communicate a risk of reproductive harm (developmental, female, and male endpoints) (FDA, 2015) in accordance with formal requirements by the US Food and Drug Administration (FDA). The FDA-approved label indicates that uses of ERIVEDGE can cause embryo-fetal death or severe birth defects. Also, studies in animal models indicate that male and female reproductive function and fertility may be impaired in patients receiving ERIVEDGE. Erivedge is a trade name of a drug that is composed of vismodegib.

Language from the FDA-approved product label (Reference ID 3762266; FDA, 2015) which meets the requirements of Section 25902 is quoted below:

Vismodegib

Reproductive Toxicity (**Developmental, Female and Male Endpoints)**

Under HIGHLIGHTS OF PRESCRIBING INFORMATION:
"**WARNING: EMBRYO-FETAL TOXICITY. *See full prescribing information for complete boxed warning.*** ERIVEDGE can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. ERIVEDGE is embryotoxic, fetotoxic, and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits, and other irreversible malformations. … Advise pregnant women of the potential risks to a fetus."

"USE IN SPECIFIC POPULATIONS. "Females and Males of Reproductive Potential: May cause amenorrhea in females. (8.3)"

Under FULL PRESCRIBING INFORMATION:
"WARNING: EMBRYO-FETAL TOXICITY. ERIVEDGE can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. ERIVEDGE is embryotoxic, fetotoxic, and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits, and other irreversible malformations. ….
[See *Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3)*]."

Under WARNINGS AND PRECAUTIONS:
"5.1 Embryo-Fetal Toxicity. Based on its mechanism of action, ERIVEDGE can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. In animal reproduction studies, vismodegib was embryotoxic, fetotoxic, and teratogenic at maternal exposures lower than the human exposures at the recommended dose of 150 mg/day …. *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*."

Under ADVERSE REACTIONS:
"**6.1 Clinical Trials Experience.** "*Amenorrhea:* In clinical trials, a total of 3 of 10 pre-menopausal women developed amenorrhea while receiving ERIVEDGE [see *Non-Clinical Toxicology (13.1)*]."

Under USE IN SPECIFIC POPULATIONS**:**
"8.1 Pregnancy. *Risk Summary.* Based on its mechanism of action and animal reproduction studies, ERIVEDGE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, oral administration of vismodegib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats *[see Data]*. There are no human data on the use of ERIVEDGE in pregnant women."

"Data
Animal Data. In an embryo-fetal developmental toxicity study, pregnant rats were administered vismodegib orally at doses of 10, 60, or 300 mg/kg/day during the period of organogenesis. Pre-and post-implantation loss were increased at doses of ≥ 60 mg/kg/day (approximately ≥ 2 times the systemic exposure (AUC) in patients at the recommended human dose), which included early resorption of 100% of the fetuses. A dose of 10 mg/kg/day (approximately 0.2 times the AUC in patients at the recommended dose) resulted in malformations (including missing and/or fused digits,

open perineum and craniofacial anomalies) and retardations or variations (including dilated renal pelvis, dilated ureter, and incompletely or unossified sternal elements, centra of vertebrae, or proximal phalanges and claws)."

"**8.3 Females and Males of Reproductive Potential.** *Contraception.*
Females. Based on its mechanism of action and animal data, ERIVEDGE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during therapy and for 7 months after the final dose of ERIVEDGE."

"Infertility.
Females. Amenorrhea can occur in females of reproductive potential. Reversibility of amenorrhea is unknown *[see Adverse Reactions (6)]*."

Under NONCLINICAL TOXICOLOGY:
"13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. Studies to assess the potential of vismodegib to affect fertility have not been conducted; however, data from repeat-dose toxicology studies in rats and dogs indicate that male and female reproductive function and fertility may be impaired in patients receiving ERIVEDGE capsule. In a 26-week toxicology study in rats, a relative decrease in percent motile sperm was observed at ≥ 15 mg/kg/day (approximately ≥ 0.3 times the AUC in patients at the recommended human dose). In dogs, increased numbers of degenerating germ cells and hypospermia were observed in young animals administered oral vismodegib for 4 weeks at ≥ 50 mg/kg/day (approximately ≥ 2 times the AUC in patients at the recommended human dose). No corresponding findings were observed in sexually mature dogs at similar doses in 13-week and 26-week toxicology studies. A decrease in the number of corpora lutea was observed in female rats administered oral vismodegib for 26 weeks at 100 mg/kg/day (approximately 0.8 times the AUC in patients at the recommended human dose)."

Under PATIENT COUNSELING INFORMATION:
"Embryo-Fetal Toxicity. Advise pregnant women of the potential risk to a fetus *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*."

Under MEDICATION GUIDE:
"ERIVEDGE can cause your baby to die before it is born (be stillborn) or cause your baby to have severe birth defects."

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 *vismodegib* 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 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 "vismodegib" 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 ERIVEDGE (vismodegib), Reference ID 3762266, revised 5-2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203388s005s006s007s008lbl.pdf