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Subject: Serious Risk with Use of Erivedge® (vismodegib) Capsules: Premature Epiphyseal Fusion

June 17, 2016

Dear Health Care Provider:

The purpose of this letter is to inform you of important new safety information for Erivedge, a Hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. The safety and effectiveness of Erivedge capsule have not been established in pediatric patients.

Serious Risk of Premature Epiphyseal Fusion with Use of Erivedge

Erivedge may cause epiphyseal closure prior to skeletal maturity.

- Cases of premature fusion of the epiphyses (growth plates) have been reported in pediatric patients taking Erivedge.
- Postnatal developmental defects including premature closure of the epiphyseal plate were observed in vismodegib treated rats. [1]

Additional information about this risk is provided in the remainder of this letter.

Additional Information on the Serious Risk

Three cases of premature epiphyseal fusion were reported in pediatric patients taking Erivedge, two within the setting of a clinical trial[2] and one with off-label use[3]. All cases were in patients with medulloblastoma whose ages were approximately 2, 5, and 7 years old at the time of Erivedge initiation. All patients completed radiation and chemotherapy prior to initiation of Erivedge. At the time when epiphyseal closure was diagnosed, the 2-year-old patient, who had recurrent disease, had received 4 months of Erivedge, while the older two patients had received 12 months of Erivedge in a clinical trial. In 2 of 3 cases, the fusion of the growth plate appeared to progress even after treatment discontinuation.

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These findings confirm the risk that was identified based on observation of irreversible closure of the femoral epiphyseal growth plate in a 26-week chronic toxicity and toxicokinetic study in rats at doses ≥ 50 mg/kg/day (corresponding to 0.4 times the exposure at steady-state $AUC_{0\text{-}24h}$ observed at the recommended dose of Erivedge in adults).[1]

Prescriber Action

Health care providers should inform patients who have not reached skeletal maturity, as well as the patient's guardian (as applicable), of this risk. Genentech is working to update the product label to reflect the risk of premature epiphyseal fusion in patients.

Reporting Adverse Events

Health care providers should report any serious adverse events suspected to be associated with the use of Erivedge to Genentech at 1-888-835-2555. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/) or by mail, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Company contact point

Should you have any questions regarding the use of Erivedge, please feel free to contact Genentech Medical Information/Communications Department at 1-800- 821-8590.

This letter is not intended as a complete description of the benefits and risks related to the use of Erivedge. Please see the accompanying, current prescribing information and Medication Guide for a complete discussion of the risks associated with Erivedge.

Sincerely,

Myriam Mendila, MD
Head of US Medical Affairs

[1] Roche GLP Study 07-1224: A 26-Week Oral Gavage Toxicity Study with GDC-0449 in Rats with an 8-Week Recovery Period
[2] Two out of three patients had 12 month exposure to vismodegib in ML28353 trial
[3] Lucas, JT, Wright KD. Vismodegib and Physeal Closure in a Pediatric Patient. Pediatr Blood Cancer.2016; Exposure information on pediatric medulloblastoma patients receiving Erivedge from off label use is not known.