Costa Rica, May 2016

Important Drug Warning: Risk of Premature Epiphyseal Fusion with Erivedge® (vismodegib)

Dear Healthcare Professional,

F. Hoffmann-La Roche Ltd. (Roche) would like to inform you of the following:

Summary

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

[1] Roche GLP Study 07-1224: A 26-Week Oral Gavage Toxicity Study with GDC-0449 in Rats with an 8-Week Recovery Period DC-0449 in Rats with an 8-Week Recovery Period

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- Erivedge® is approved for use in adult patients with advanced basal cell carcinoma where surgery is inappropriate.

- Erivedge® is not approved for pediatric use.

- Erivedge® could cause epiphyseal closure prior to skeletal maturity.

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

This information has been informed to the Health Authority.

Further information on the safety concern and recommendations

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

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 steady-state $AUC_{0\text{-}24h}$ observed in patients).[1]

Healthcare providers or investigators should inform patients, as well as a patient's guardian (as applicable), who have not reached skeletal maturity, of this risk.

Roche is working to update the prescribing information to reflect the risk of premature epiphyseal fusion in patients.

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[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.

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Call for reporting

Health care professionals should report any serious adverse events suspected to be associated with the use of Erivedge® to cac.farmacovigilancia@roche.com.

Company contact point

Should you have any questions regarding the use of Erivedge®, please feel free to contact us at: cac.medical_info@roche.com.

Sincerely,

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