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IMPORTANT SAFETY UPDATE - ERIVEDGE® (vismodegib)
Risk of Premature Epiphyseal Fusion

30 May 2016

Dear Doctor,

Roche Products (New Zealand) Limited ("Roche") would like to inform you of safety updates to Erivedge.

Summary

- Cases of premature fusion of the epiphyses (growth plates) have been reported in paediatric patients with the use of Erivedge.
- Postnatal developmental defects including premature closure of the epiphyseal plate were observed in vismodegib treated rats. [1]
- Erivedge is approved for use in adult patients with metastatic or locally advanced basal cell carcinoma where surgery and/or radiation therapy are not appropriate.
- Erivedge is not approved for paediatric use.
- Erivedge could cause epiphyseal closure prior to skeletal maturity.

Further Information on the Safety Concern and Recommendations

Three cases of premature epiphyseal fusion in paediatric 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.

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

Doctors should inform the patients and guardians of patients who have not reached skeletal maturity of this risk.

Updated Safety Information in the Erivedge Data Sheet

The Precautions and Post-Marketing sections of the Erivedge Data Sheet have been updated to include premature fusion of the epiphyses reported in paediatric patients exposed to Erivedge. If you have any questions or require additional information regarding the use of Erivedge please contact Roche Medical Information on 0800 276 243 or email at auckland.medinfonz@roche.com

Reporting Adverse Events

Roche will continue to monitor the safety of Erivedge through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation. Please report any suspected adverse events via email to Roche Drug Safety at nz.drugsafety@roche.com. Alternatively, this information may be reported to the Centre for Adverse Reactions Monitoring (CARM) in Dunedin by telephone on (03) 479 7247, by fax on (03) 479 7150, online at https://nzphvc.otago.ac.nz/reporting or by email to nzphvc@otago.ac.nz

Sincerely

Jan Campbell
Director Medical Affairs,
Roche Products (New Zealand) Limited

[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.

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