



Costa Rica, February 2017

Important Drug Warning: Risk of Dupuytren's Contracture and Plantar Fascial Fibromatosis with Zelboraf® (vemurafenib)

Dear Healthcare Professional,

Roche would like to inform you of the following:

*Summary*

- Cases of Dupuytren's contracture and plantar fascial fibromatosis have been reported with Zelboraf use.
- The majority of cases were mild or moderate in severity. However, severe, disabling cases of Dupuytren's contracture have also been reported.
- Dupuytren's contracture and plantar fascial fibromatosis should be managed using temporary interruption or treatment discontinuation of Zelboraf, as outlined in the current Zelboraf label.

*Further information on the safety concern and recommendations*

The reported cases of Dupuytren's contracture seen with Zelboraf were characterized by thickening or appearance of visible cords in the palm of one or both hands. The median time to onset was 224 days from the initial dose of Zelboraf. In the majority of patients, the event persisted when Zelboraf treatment was maintained, while in cases where Zelboraf was either interrupted or discontinued, the majority of patients had improvement of symptoms or resolution of the event. One patient with a pre-existing Dupuytren's contracture experienced an exacerbation of the condition after Zelboraf use. In addition to Dupuytren's contracture, rare



cases of mild and moderate plantar fascial fibromatosis were also reported with Zelboraf use. Sequential involvement of the hands and feet was observed in one case.

Healthcare providers should inform patients of this risk and should exercise caution in patients with pre-existing Dupuytren's contracture and plantar fascial fibromatosis. Healthcare providers are advised to follow the dose modification guidance for adverse events as outlined in the Zelboraf label: for moderate and severe fibromatosis, it is recommended that treatment with Zelboraf is interrupted until event is resolved or improved; dose should be reduced by 240 mg increment at resumption of treatment. Treatment interruption with dose reduction should be attempted twice and permanently discontinued if no resolution or improvement. Dose reduction resulting in a dose below 480 mg twice daily is not recommended.

Roche is working to update the product information as soon as possible to reflect the risk of Dupuytren's contracture and plantar fascial fibromatosis.

#### *Call for reporting*

Health care professionals should report any adverse events suspected to be associated with the use of Zelboraf. The email [cac.farmacovigilancia@roche.com](mailto:cac.farmacovigilancia@roche.com) is available to report any adverse event to the Local Safety Unit.

#### *Company contact point*

Should you have any questions regarding the use of Zelboraf, please feel free to contact us at: [cac.medical\\_info@roche.com](mailto:cac.medical_info@roche.com).

Sincerely,

Roche Servicios S.A.