

June, 2017

**IMPORTANT  
DRUG  
WARNING**

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**Subject: Risk of Dupuytren's Contracture and Plantar Fascial Fibromatosis with  
Zelboraf® (vemurafenib)**

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Dear Health Care Provider:

The purpose of this letter is to inform you of new important safety information for Zelboraf, indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Zelboraf is not indicated for treatment of patients with wild-type BRAF melanoma.

***Serious Risks with Use of Zelboraf***

- Cases of new onset, as well as worsening of pre-existing, 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 (see Section 2.3, Dose Modifications).

Genentech is working closely with the U.S. Food and Drug Administration (FDA) to update the product label to reflect the risk of Dupuytren's contracture and plantar fascial fibromatosis.

***Additional Information on the Serious Risks***

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 other cases where Zelboraf was either interrupted or discontinued, the majority of patients had improvement of symptoms or resolution of the event. One patient with 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.

**Prescriber Action**

Health Care Providers should inform patients about these risks and should exercise caution when prescribing Zelboraf to treat patients with pre-existing Dupuytren's contracture and plantar fascial fibromatosis. Health Care Providers are advised to follow the dose modification guidance for adverse events as outlined in the current Zelboraf label (see Section 2.3, Dose Modifications).

**Reporting Adverse Events**

Health Care Providers and patients are encouraged to report adverse events in patients taking Zelboraf 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**

Should you have any questions about the information in this letter or the safe and effective use of Zelboraf, please feel free to contact us at: 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 Zelboraf. Please refer to the enclosed full Prescribing Information, including Medication Guide, for additional Important Safety Information.

This letter is being sent in agreement with the FDA pursuant to requirements set forth in 21 CFR 200.5.

Sincerely,



Edith A Perez, M.D.

VP, Head of BioOncology, U.S. Medical Affairs