Genentech
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080

IMPORTANT DRUG WARNING

March 2014

Subject: **Risk of liver injury reported with Zelboraf® (vemurafenib)**

Dear Healthcare Professional,

Genentech, a member of the Roche Group, would like to inform you of the following important safety information for Zelboraf:

Summary

- Liver injury, including two cases of severe liver injury, has been reported with Zelboraf. There were no risk factors or populations at risk that were identified.
- Prescribers are reminded to monitor transaminases, alkaline phosphatase, and bilirubin before initiation of Zelboraf treatment and monthly during treatment, or as clinically indicated.
- Liver injury should be managed using dose reduction, temporary interruption, or treatment discontinuation of Zelboraf, as indicated in the current Zelboraf label (Guidance on dose modifications for adverse events).

Zelboraf is indicated for the treatment of BRAF V600E mutation-positive unresectable or metastatic melanoma as detected by an FDA-approved test. Zelboraf is not indicated for use in patients with wild-type BRAF melanoma.

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

Further information on the safety concern and recommendations

Liver injury has been reported with Zelboraf treatment. Based on an analysis of liver-related adverse events reported with Zelboraf use, 63 cases out of an estimated 20,000 patients treated with Zelboraf were identified as having experienced drug-induced liver injury (DILI) using the clinical chemistry criteria for DILI developed by an international DILI Expert Working Group[1], where DILI is defined as any of the following:

- More than or equal to fivefold elevation above the upper limit of normal (ULN) for alanine aminotransferase (ALT)

- More than or equal to twofold elevation above the ULN for alkaline phosphatase (ALP) (particularly with accompanying elevations in concentrations of 5'-nucleotidase or γ-glutamyl transpeptidase in the absence of known bone pathology driving the rise in ALP level)
- More than or equal to threefold elevation in ALT concentration and simultaneous elevation of bilirubin concentration exceeding 2X ULN

There were no reported deaths among the 63 cases of liver injury. There were two severe cases (based on the DILI severity index by the same Expert Working Group), both reported as hepatic failure; the outcome of one case of severe liver injury was reported as completely resolved with Zelboraf discontinuation while the outcome of the second severe liver injury case is not available at this time.

This finding further characterizes the hepatotoxicity risk as liver injury, compared to that currently listed in the Zelboraf label, liver laboratory abnormalities. Healthcare providers should monitor transaminases, alkaline phosphatase, and bilirubin before initiation of treatment and monthly during treatment, or more often as clinically indicated. Liver injury should be managed using dose reduction, temporary interruption, or treatment discontinuation of Zelboraf, as indicated in the current Zelboraf label guidance on dose modifications for adverse events.

Genentech is working closely with health authorities to update the product label to reflect the risk of liver injury.

Call for reporting

Healthcare professionals should report any case of liver injury and other serious adverse events suspected to be associated with the use of 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 mailed, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

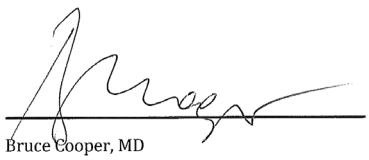
Company contact point

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

Please note that this presentation of the risk profile for Zelboraf is not comprehensive. Please refer to the enclosed Zelboraf® full prescribing information, including the Medication Guide, for a complete discussion of the risks associated with ZELBORAF® (vemurafenib) oral tablet.

Sincerely,

Genentech, a Member of the Roche Group



Bruce Cooper, MD
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[1] Aithal, GP, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharm Ther*. 2011 June; 89(6):806-15