Important Drug Warning: Risk of liver injury reported with Zelboraf® (vemurafenib)

02/03/2014

Dear Healthcare Professional,

Hoffmann-La Roche Ltd/Genentech Inc. would like to inform you of the following:

Summary

- Liver injury, including cases of severe liver injury, has been reported with Zelboraf.
- 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).

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

This information is being sent in agreement with the Saudi Food and Drug Authority (SFDA).

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 2× 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 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.

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

Zelboraf is indicated for the treatment of BRAF V600 /V600E [adjust according to approved indication] mutation-positive unresectable or metastatic melanoma.

Call for reporting

Health care professionals should report any serious adverse events suspected to be associated with the use of Zelboraf to:

Local Safety Responsible
Hoffmann La-Roche
Saudi Import Company
Najoud Centre, Gate A, 1st Floor.
Prince: Mohamed Bin Abdulaziz St.
Phone: 0096612 2847190
Mobile: 00966561968563
Email: hazem.dajani@roche.com

Or to The National Pharmacovigilance & Drug safety Centre (NPC) Saudi Food and Drug Authority (SFDA)
Toll free number: 8002490000
Fax: +966-11-2057662
Email: Npc.drug@sfda.gov.sa
Online: http://ade.sfda.gov.sa/

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

Company contact point

Should you have any questions regarding the use of Zelboraf, please feel free to contact us at:
Hoffmann La-Roche
Saudi Import Company
Najoud Centre, Gate A, 1st Floor.
Prince: Mohamed Bin Abdulaziz St.
Phone: 0096612 2847190
Mobile: 00966561968563
Email: hazem.dajani@roche.com

Sincerely Yours,

Hazem Al-Dajani	Naser Al-Rajhi	Tamer Elmahallawy
Local Safety Responsible	Scientific office director	Medical Director
18 March 2014	19. March. 2014	18 3 2014