Costa Rica, February 14th, 2014

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

Dear Healthcare Professional,

F. Hoffmann-La Roche Ltd would like to inform you of the following of the product Zelboraf, indicated for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

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 insert (Guidance on dose modifications for adverse events).

This information has been informed to the National Sanitary Authorities.

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

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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 to update the product label to reflect the risk of liver injury.

Further Information
If you have any questions or require additional information regarding the use of Zelboraf®, please contact cac.medical_info@roche.com

Call for reporting
Health care professionals should report any serious adverse events suspected to be associated with the use of Zelboraf to: cac.farmacovigilancia@roche.com or +506-2298-1500 / US toll free 1-888-670-4123.

Company contact point
Should you have any questions regarding the use of Zelboraf, please feel free to contact us under the below address: cac.medical_info@roche.com

Sincerely,

Roche Servicios S.A.

Should you have any questions or require additional information regarding the use of Zelboraf®, please contact: cac.medical_info@roche.com

To report an adverse event of Zelboraf® or any other Roche product, please contact: cac.farmacovigilancia@roche.com