Health Canada Endorsed Important Safety Information on ZELBORAF® (vemurafenib)

Date: April 7, 2014

Dear Health Care Professional:

Subject: Association of ZELBORAF® (vemurafenib) Use with Drug Induced Liver Injury (DILI)

Hoffmann-La Roche Limited (Roche Canada), in consultation with Health Canada, would like to inform you of important new safety information regarding the risk of Drug Induced Liver Injury (DILI) reported with ZELBORAF.

ZELBORAF is indicated as a monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. A validated test is required to identify BRAF V600 mutation status.

- Drug Induced Liver Injury (DILI), including cases of severe liver injury, has been reported with ZELBORAF.
- The ZELBORAF Product Monograph will be updated to include appropriate information regarding the risk of DILI and physicians should discuss the currently available information regarding benefits and risks of ZELBORAF with their patients.
- 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.

Based on Roche's analysis of liver related adverse events reported with ZELBORAF use, as of September 26, 2013, 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 above ULN 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.

The Product Monograph for ZELBORAF will be updated by Roche Canada, in collaboration with Health Canada, to include appropriate information regarding the risks of DILI. Once the updates are complete the updated Product Monograph will be available on the Health Canada website (http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp) and on the Roche Canada website http://rochecanada.com/PMs/Zelboraf/Zelboraf_PM_E.pdf.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of liver injury or other serious or unexpected adverse reactions in patients receiving ZELBORAF should be reported to Roche Canada or Health Canada.

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To correct your mailing address or fax number, contact Hoffmann-La Roche Limited.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax

For other health product inquiries related to this communication, contact Health Canada at:
Marketed Health Products Directorate (MHPD)
E-mail: mhpd_dpsc@hc-sc.gc.ca
Tel: (613) 954-6522
Fax: (613) 952-7738

Should you have any questions or require additional information regarding the use of ZELBORAF, please contact the Drug Information Department at Hoffmann-La Roche Limited at 1-888-762-4388, Monday to Friday, between 8:30 a.m. and 4:30 p.m. (Eastern Standard Time).

Original signed by

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Reference: *[1]Case Definition and Phenotype Standardization in Drug-Induced Liver Injury, GP Aithal, PB Watkins, RJ Andrade, D Larrey et al., Clin Pharmacol Ther., 89(6):806-15, 2011.*