Important Safety Information on ZELBORAF® (vemurafenib) and the Risk of Radiation Sensitization or Radiation Recall Reaction

Roche

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Audience
Medical oncologists, radiation oncologists and other health care professionals providing care to cancer patients including those working in hospitals, cancer clinics and pharmacies.

Key messages

- **Cases of radiation sensitization and cases of radiation recall reactions have been reported in patients treated with radiation prior to, during, or following ZELBORAF (vemurafenib) treatment. Most cases were cutaneous in nature but some cases involving visceral organs had fatal outcomes.**
- **It is recommended that ZELBORAF not be used concomitantly with radiation therapy, unless the potential benefit justifies the potential risk to the patient.**
- **New warnings have been added to the Canadian prescribing and consumer information for ZELBORAF advising of this serious risk.**

What is the issue?
Cases of radiation sensitization and cases of radiation recall reactions have been reported in patients treated with radiation prior to, during, or following ZELBORAF (vemurafenib) treatment.

Products affected
ZELBORAF (vemurafenib) tablets

Background information
ZELBORAF (vemurafenib) is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, as detected by a validated test.

An analysis of safety information concluded that potentiation of radiation toxicity, either in the form of radiation sensitization or radiation recall, is a risk associated with vemurafenib treatment. This conclusion is based primarily on 20 cases of radiation toxicity involving vemurafenib; 3 of the 20 cases had fatal outcomes. The nature and severity of the events in all 20 cases were evaluated as worse than expected for the normal tissue tolerance to therapeutic radiation. Most cases were cutaneous in nature but some cases involved visceral organs (e.g. pneumonitis,

esophagitis, cystitis, brain and liver necrosis). In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day (hypofractionated regimens). The incidence of radiation-related injuries seen in the vemurafenib Phase III and Phase IV clinical trials was 5.2% and 6% respectively (CI 1.71-11.74, 3.14 – 10.25).

Information for consumers
ZELBORAF (vemurafenib) is used in adult patients to treat a type of skin cancer (malignant melanoma) that has a change (mutation) in the "BRAF" gene and that cannot be removed by surgery or has spread to other parts of the body (unresectable or metastatic).

Before you use ZELBORAF, talk to your doctor or pharmacist if you have received radiation treatment or are planning to receive radiation treatment. ZELBORAF may increase your body's sensitivity to radiation therapy. Worsening of radiation treatment side effects has been reported in patients who are treated with radiation before, during, or after ZELBORAF treatment. This can occur on the area that was treated with radiation, such as the skin, esophagus, bladder, liver, rectum, brain and lungs. Tell your doctor right away if:

- You develop skin rash, blistering, peeling or discoloration of the skin
- You have shortness of breath, which may be accompanied by a cough, fever or chills (pneumonitis)
- You have difficulty or pain when swallowing, chest pain, heartburn or acid reflux (esophagitis)

Patients and caregivers should contact their health care professional for more information.

Information for health care professionals
It is recommended that ZELBORAF (vemurafenib) not be used concomitantly with radiation therapy, unless the potential benefit justifies the potential risk to the patient.

Please refer to the ZELBORAF Canadian product monograph for full prescribing and safety information. The current ZELBORAF Canadian product monograph can be found on Health Canada's Web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php).

Action taken by Health Canada
Health Canada, in collaboration with Hoffmann-La Roche Limited, has updated the Canadian prescribing and consumer information for ZELBORAF (vemurafenib) to reflect the potential of risk radiation sensitization and radiation recall. Health Canada is also communicating this important safety information to health care professionals and to the public through its Healthy Canadians Web site (www.healthycanadians.gc.ca) and MedEffect™ e-Notice.

Report health or safety concerns
Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any case of radiation sensitization or radiation recall or other serious or unexpected side effects in patients receiving ZELBORAF (vemurafenib) should be reported to Hoffmann-La Roche Limited or Health Canada.

Hoffmann-La Roche Limited
Drug Safety Department
7070 Mississauga Road
Mississauga, Ontario, L5N 5M8
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Fax: 905-542-5864
E-mail: mississauga.drug_safety@roche.com

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 for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, please contact Health Canada at:

Marketed Health Products Directorate
E-mail: mhpd_dpsc.public@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

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If you require this information in an accessible format, please contact Roche at 1-800-561-1759.