Roche

Potentiation of Radiation Toxicity associated with Zelboraf® ▼ (vemurafenib)

19th October 2015

Dear Healthcare Professional,

Roche Products (Ireland) Limited, in agreement with the European Medicines Agency and the Health Products Regulatory Authority would like to inform you of the following:

Summary

- Severe cases of radiation-related injuries, some with fatal outcome, have been reported in patients treated with radiation either before, during, or following treatment with Zelboraf.
- Most cases were cutaneous in nature but some cases involved visceral organs.
- Zelboraf should be used with caution when given before, during, or following radiation treatment.

Further information on the safety concern

A safety analysis of radiation-related adverse events reported with vemurafenib use concluded that potentiation of radiation treatment toxicity constitutes an adverse drug reaction for vemurafenib. This conclusion is based on 20* cases of radiation injuries adjudicated as radiation recall (n=8 cases) and radiation sensitisation (n=12 cases). 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. 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). In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day.

* Exposure information on patients receiving both Zelboraf and radiation therapy is not known.

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- **Radiation recall**

The 8 cases of radiation recall showed acute inflammation confined to previously irradiated area, triggered by Zelboraf administration ≥ 7 days after completion of radiotherapy. Five out of 8 cases (62%) affected the skin while the remaining cases involved the lung (n=2), and urinary bladder (n=1). Cutaneous reactions ranged from erythema, hyperkeratosis, eczematous, vesicular, and ulcerative lesions. In the patients with cutaneous reactions, the mean time interval between the end of radiotherapy and the start of Zelboraf treatment was 31 days (range 21-42); for non-cutaneous recall reactions, the interval was 26 and 28 days for lung and 1460 days for the urinary bladder. The mean time to onset of radiation recall skin reaction after Zelboraf initial dose is 12 days (range 7-21 days); 24 days for pneumonitis; and 1 day for cystitis.

- **Radiation sensitisation**

The 12 cases of radiation sensitisation showed potentiation of radiation reaction evidenced by the greater than expected severity of the reaction for local radiation injury. Of the 12 cases, 9 events involved the skin, 3 events involved the oesophagus, and one event each for liver and rectum. The nature of skin radiation sensitisation is similar to that seen in radiation recall skin reactions. Except for one case, all cases were either dosed concomitantly with radiation or within 3 days after completion of radiotherapy. When reported, the time to onset of the reaction following initiation of radiation therapy or Zelboraf treatment ranged from 3 to 27 days (mean = 10 days, median = 8.5 days).

There were 3 cases with fatal outcome: one case was a patient who developed radiation necrosis of the liver 10 weeks after receiving 20 Gy of fractionated radiation over the thoracic spine while on Zelboraf. Two other cases were patients who developed radiation oesophagitis, one of whom was reported to have worsening of grade 1 oesophagitis to grade 4, 10 days after the patient was started on Zelboraf. Information on the other case of fatal oesophagitis is limited.

The product information will be updated with information of this risk of potentiation of radiation toxicity.

Zelboraf is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Call for reporting

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

Healthcare professionals are asked to report any suspected adverse reactions in accordance with the national spontaneous reporting system:

Suspected adverse reactions should be reported to the HPRA using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling (01) 676 4971.

Adverse events should also be reported to the Drug Surveillance Centre in Roche Products (Ireland) Limited by mail, telephone (01-4690700), fax (01-4690793) or email (Ireland.drug_surveillance_centre@roche.com).

Company contact point

Should you have any questions regarding the use of Zelboraf, please feel free to contact Roche Medical Information by mail, telephone (01-4690700), fax (01-4690791) or email (ireland.druginfo@roche.com).

Yours sincerely,

Dr. Michal Starnawski
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