ZALTRAP 25 mg/ml concentrate for solution for infusion EU/1/12/814/003

Direct Healthcare Professional Communication

ZALTRAP (aflibercept): information on the risk of osteonecrosis of the jaw

Dear Healthcare professional, *16TH March 2016*

Sanofi-aventis Ireland Limited T/A SANOFI in agreement with the European Medicines Agency and the Health Products Regulatory Authority would like to inform you of the following:

Summary

- **Osteonecrosis of the jaw (ONJ) has been reported in cancer patients treated with Zaltrap.**
- **Several of these patients had received concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk.**
- **Zaltrap treatment may be an additional risk factor for the development of ONJ.**
- **This risk should be considered, particularly when Zaltrap and intravenous bisphosphonates are administered concomitantly or sequentially.**
- **Invasive dental procedures are also an identified risk factor for ONJ. A dental examination and appropriate preventive dentistry should be considered before starting treatment with Zaltrap.**
- **Invasive dental procedures should, if possible, be avoided in patients treated with Zaltrap and who have previously received or are receiving intravenous bisphosphonates.**

Further information on the safety concern

ZALTRAP (aflibercept) in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy is indicated in adults with metastatic colorectal cancer (MCRC) that is resistant to, or has progressed after, an oxaliplatin-containing regimen.

A meta-analysis of 3 phase 3 studies ((EFC10262/VELOUR, EFC10261/VITAL, EFC10547/VANILLA) found an overall frequency of ONJ of 0.2% (3 patients, N=1333) in patients treated with aflibercept and <0.1% (1 patient, N=1329) in patients treated with placebo.

As of 03-Aug-2015, it is estimated that Zaltrap has been administered to more than 22 700 cancer patients worldwide. Cumulatively up to 03-Aug-2015, Sanofi has received eight reports of ONJ occurring in patients receiving Zaltrap. Three of these cases were

reported with concomitant use of bisphosphonates, for which ONJ is an identified risk. Three cases had invasive dental procedures. Of the three who had dental procedure, two were also on concomitant bisphosphonates, or had been recently treated with bisphosphonate. None of the cases had fatal outcome.

Given the findings in clinical studies, the review of the reported cases, and a potential class effect of antiangiogenic agents targeting VEGF pathways, the Summary of Product Characteristics and Patient Information Leaflet have been updated to include new safety information on ONJ and provide recommendations on the management of patients.

Invasive dental procedures are an identified risk factor for ONJ. Therefore, a dental examination and appropriate preventive dentistry should be considered before starting treatment with Zaltrap.

Caution should be exercised when Zaltrap and intravenous bisphosphonates are administered concomitantly or sequentially.

Invasive dental procedures should be avoided, if possible, in patients treated with Zaltrap, who have previously received or are receiving intravenous bisphosphonates.

Further information

Detailed information on Zaltrap is available on the website of the European Medicines Agency (EMA):

http://www.ema.europa.eu/ema/

Please share this information with relevant colleagues and healthcare personnel.

Call for reporting

▼This medicinal product is subject to additional monitoring. This is intended to facilitate early identification of new safety information. Healthcare professionals are reminded that any suspected adverse events should be reported to the National Spontaneous Reporting System according to the National Regulation.

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.

Company contact point

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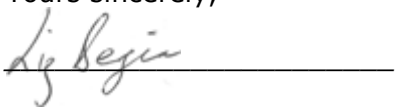
Yours sincerely,



Dr Liz Bergin
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