16th March 2016

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

Dear Healthcare professional,

Sanofi, in agreement with the European Medicines Agency (EMA) and Medicine and Healthcare products Regulatory Agency (MHRA) 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 and the recommendations

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 3 August 2015, it is estimated that Zaltrap has been administered to more than 22 700 cancer patients worldwide. Cumulatively up to 3 August 2015, Sanofi has received eight reports worldwide 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 vascular endothelial growth factor (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 health care personnel.

Call for reporting

▼ This medicinal product is subject to additional monitoring. This is intended to facilitate early identification of new safety information

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme. Please report

- All suspected ADRs that are serious or result in harm. (Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason).
- All suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼

It is easiest and quickest to report ADRs online via the Yellow Cards website: www.mhra.gov.uk/yellowcard

Alternatively, prepaid Yellow Cards for reporting are available:

- By writing to FREEPOST YELLOW CARD (no other address details necessary)
- By emailing yellowcard@mhra.gsi.gov.uk
- At the back of the British National Formulary (BNF)
- By telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- Or by downloading and printing a form from the Yellow Card section of the MHRA website.

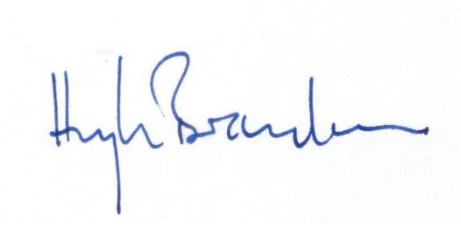
When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates and product brand name.

Adverse events arising from the use of medicines manufactured by Sanofi may also be reported to the **Sanofi UK Pharmacovigilance** department at: Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS; Tel: 01483 554242; Fax: 01483 554806;
Email: uk-drugsafety@sanofi.com

Company contact point

Should you have any question or require additional information, please contact **Medical Information** at Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS, UK; Tel: 0845 372 7101;
Email: uk-medicalinformation@sanofi.com

Yours faithfully,



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