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Worldwide Biopharmaceutical Businesses

30th November 2010,

Osteonecrosis of the jaw in cancer patients treated with sunitinib (Sutent) and concomitant or previous use of bisphosphonates

Dear Healthcare Professional,

Summary

This letter is to inform you of an important update to the safety information regarding the use of Sutent (sunitinib malate).

- **Cases of osteonecrosis of the jaw have been reported in cancer patients in association with sunitinib (Sutent) treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.**
- **Sutent treatment may be an additional risk factor for the development of osteonecrosis of the jaw.**
- **This potential risk should be particularly considered when Sutent and bisphosphonates are administered simultaneously or sequentially.**
  Dental examination and appropriate preventive dentistry should be considered prior to treatment with Sutent. In patients who have previously received or are receiving i.v. bisphosphonates invasive dental procedures should be avoided, if possible.

The communication of this information has been agreed with the European Medicines Agency (EMA) and the Irish Medicines Board (IMB).

Further information on the safety concern

Sutent is a medicinal product containing sunitinib malate. It is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) in adults after the failure of imatinib mesylate due to resistance or intolerance, the treatment of advanced/metastatic renal cell carcinoma in adults (MRCC).

From 26 January 2006 (International Birth Date [IBD]) through 31 January 2010, the worldwide estimated exposure to Sutent is 101400 including post-marketing and clinical trials patients.

Overall, a total of 27 cases of ONJ have been reported as of 31 January 2010 associated with Sutent, including both clinical trials and post marketing cases. Cases of ONJ have been reported in cancer patients treated with Sutent, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk.

The potent anti-angiogenic activity of sunitinib might amplify the inhibition of bone remodelling exerted by aminophosphonates entrapped within the osteonecrotic mineral matrix and antagonize mucosal healing which may result in exposure of bone to infectious agents during treatment with sunitinib. Such soft- tissue damage may play a role in the pathogenesis of osteonecrosis of the jaw.

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Caution should therefore be exercised when Sutent and bisphosphonates are administered simultaneously or sequentially. Dental examination and appropriate preventive dentistry should be considered prior to treatment with Sutent. In patients who have previously received or are receiving i.v. bisphosphonates invasive dental procedures should be avoided, if possible.

Further information on recommendation to healthcare professionals:

In order to minimize the above identified risk, the following text has been added to the Sutent Summary of Product Characteristics (SPC):

SPC

4.4 Warnings and precautions

Cases of ONJ have been reported in patients treated with SUTENT. The majority of cases occurred in patients who had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when SUTENT and i.v. bisphosphonates are used either simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor.
Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered.
In patients who have previously received or are receiving i.v. bisphosphonates, invasive dental procedures should be avoided, if possible.

4.8 Undesirable effects

Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with SUTENT, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to i.v. bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4).

CALL FOR REPORTING

Healthcare professionals should report any serious adverse events suspected to be associated with the use of Sutent to Pfizer at 1800 633363. Alternatively, this information may be reported to IMB by calling: (01) 6764971, using on-line reporting forms at: www.imb.ie or Using post-paid Report Cards (Yellow Cards) e-mail: imbpharmacovigilance@imb.ie

For further information or any questions on ONJ associated with the use of Sutent, please contact Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS or Tel.: 1800 63363.

Sincerely,

Dr. Declan O'Callaghan
Medical Director
Pfizer Healthcare Ireland