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Committee for Medicinal Products for Human Use (CHMP)

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Active substance(s): zoledronic acid (indicated for cancer and fractures)

Procedure No. EMEA/H/C/PSUSA/00003149/201608

Period covered by the PSUR: 1 September 2015 to 31 August 2016

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for zoledronic acid (indicated for cancer and fractures), the scientific conclusions of CHMP are as follows:

The analysis of the individual safety reports from clinical trials, spontaneous reports and literature retrieved 62 cases of osteonecrosis of other anatomical sites in association with zoledronic acid, with the majority of events occurring in the hip/femur (46). The occurrence of osteonecrosis is multifactorial and is associated with various risk factors. There are no site specific risk factors for osteonecrosis apart from additional oral risk factors for osteonecrosis of the jaw. There is preponderance of specific location (head of femur, humerus and medial condyle of femur) due to local anatomical features. The cases from safety database did report multiple risk factors including underlying malignancy, bone metastases; concomitant therapy with steroids, angiogenesis inhibitors, radiotherapy but the exact underlying cause for the osteonecrosis was not ascertained. The reports of osteonecrosis at other sites with zoledronic acid suggest similarity in reporting frequency (femur>knee>humerus) as compared to the commonly affected sites of osteonecrosis based on anatomical factors. The time to onset for occurrence of osteonecrosis also has similar pattern when compared to osteonecrosis of the jaw/external auditory canal. The contributive role of zoledronic acid therapy in these cases could not be excluded. Therefore, the product information should be updated to reflect in sections 4.4 and 4.8 of the SmPC a warning on osteonecrosis of other anatomical sites and add this adverse reaction with a frequency very rare. The package leaflet is updated accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for zoledronic acid (indicated for cancer and fractures) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing zoledronic acid (indicated for cancer and fractures) is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.