NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

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This notification is a referral under Article 20 of Regulation (EC) No 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission (EC):

Product name Procedure name	Xofigo Xofigo (radium-223 dichloride)
Active substance	Radium Ra 223 dichloride
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	Bayer AG

Xofigo is a therapeutic alpha particle-emitting pharmaceutical. Its active moiety radium-223 (as radium-223 dichloride) mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/μm) leads to a high frequency of double-strand DNA breaks in adjacent tumour cells, resulting in a potent cytotoxic effect. Additional effects on the tumour microenvironment including osteoblasts and osteoclasts also contribute to the *in vivo* efficacy. The alpha particle range from radium-223 is less than 100 μm (less than 10 cell diameters) which minimises damage to the surrounding normal tissue.

Xofigo (radium-223 dichloride) was authorised in the EU under the centralised procedure in November 2013. It is currently authorised for the treatment of adults with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastases.

In November 2017, the European Commission was informed of the marketing authorisation holder's intention to unblind an ongoing Phase 3 study evaluating the safety and efficacy of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic CRPC (ERA-223 study[1]). The unblinding of the study follows from a recommendation by the independent data monitoring committee (IDMC), that had observed significant imbalances concerning treatment emergent fractures, symptomatic skeletal events-free survival (SSE-FS), and total deaths events between two blinded treatment arms. The analysis of the IDMC was based on uncleaned data available as of 5 September 2017 and (prior to survival sweep) found that, in this clinical trial, the incidences of treatment emergent fractures and deaths were increased in the treatment arm

[1] Study 15396 (ERA-223); NCT02043678; A phase III randomised, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

(radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone).

This study evaluates Xofigo in an unauthorised treatment combination with abiraterone acetate and prednisone/prednisolone in a patient population with asymptomatic or mildly symptomatic prostate cancer.

In the framework of a discussion in Pharmacovigilance Risk Assessment Committee (PRAC) triggered by the submission of the above information, some concerns were raised about the impact of this emerging safety data on the approved indication of Xofiga. Therefore, the above mentioned findings from the ERA 223 clinical trial warrant a thorough review in the context of all available data (including evidence from non authorised use that might impact the authorised use) related to radium-223 dichloride in order to assess their potential impact on the benefit-risk balance of Xofigo.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the impact of the above emerging safety data on the benefit risk balance for the centrally authorised medicinal product Xofigo (radium Ra 223 dichloride). The EC requests the Agency to give its opinion by 31 May 2018 on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

[redacted]

29/11/2017

Signed Date

Olga Solomon
Head of Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General