30 November 2017
EMA/PRAC/790594/2017

PRAC List of questions

To be addressed by the marketing authorisation holder

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Procedure number: EMEA/H/A-20/1459/C/002653/0028

Invented name: Xofigo

INN/active substance: radium Ra223 dichloride

Marketing authorisation holder: Bayer AG

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Questions

The marketing authorisation holder (MAH) is requested to address the following questions:

Question 1. Please provide the marketing status and exposure to Ra223 dichloride in European Union (EU) Member States (MS), Iceland and Norway, and worldwide. This should include data from completed and ongoing studies and all post-marketing sources. Please provide any data, in addition to the REASSURE study[1], on extent of exposure to the Ra223 dichloride and abiraterone combination in post-marketing use.

Question 2. Provide an analysis of the complete dataset from the ERA 223 study[2] following the full survival sweep, and the reasons for the differences in outcome between the two arms (including type and localization of fractures as well as number, size and type of metastases). This should include all relevant safety endpoints, including mortality, fractures, the skeletal symptomatic events endpoint and its components. Please provide the causality assessment for all deaths. Available information regarding the Ra223 specific effects should be discussed.

Question 3. Please provide an analysis of the time to onset for fractures and death in the ERA 223 study. Discuss the timing of these events in the two study arms and any conclusion on the risk period. Provide an analysis of fractures depending on whether or not patients received bone modifying agents. Discuss potential mechanisms for the increased risk of fractures, including a possible pharmacodynamic interaction between Ra223 and abiraterone and prednisone/prednisolone.

Question 4. Provide Kaplan Meier curves for survival and fractures for all randomised controlled trials for Ra223 dichloride. An overview about data on combined endpoints and single separate endpoints, overall fractures, pathological and non-pathological fractures should also be presented and discussed.

Question 5. Please provide an overview of all clinical trials evaluating the radium Ra223 dichloride – abiraterone combination treatment, their current study status, populations involved and study questions addressed.

Question 6. Provide a comprehensive discussion of:

a) Possible reasons for the different results from the ERA 223 study and the pivotal phase III trial ALSYMPCA, including differences in disease (e.g. size and number of metastases), baseline characteristics, concomitant treatments and any other relevant factors, including differences between the two studies in exposure to Ra223 (i.e. number of injections administered).

b) Potential reasons for the conflicting data from the ERA 223 study and other studies and international early access programs.

c) The safety and efficacy of the combination of Ra223 dichloride and abiraterone with a particular focus on fractures and survival.

Question 7. Please discuss whether data on the combination of Ra223 dichloride and abiraterone from the ERA 223 study are relevant to the combination of Ra223 dichloride with other anti-androgens. Discuss relevant data from studies where some patients treated with Ra223 dichloride also received anti-androgens.

[1] Observational Study for the Evaluation of Long-term Safety of Radium-223 Used for the Treatment of Metastatic Castration Resistant Prostate Cancer (REASSURE)
[2] 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)

Question 8. Provide a critical appraisal of the overall impact of the above data on the benefit-risk balance of Ra223 dichloride in its authorised indication. Include a discussion of whether any amendments to the product information or the risk management plan are needed.