Annex IV

Scientific conclusions

radium Ra223 dichloride

Scientific conclusions

Analyses of uncleaned preliminary data of a clinical trial evaluating Xofigo in combination with abiraterone acetate and prednisone/prednisolone in a patient population with asymptomatic or mildly symptomatic prostate cancer (ERA 223), found that the incidences of treatment emergent fractures and deaths were increased in the treatment arm (radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone).

In view of the significance of the findings of the ERA 223 clinical trial, it was considered that they should be thoroughly reviewed in the context of all available data related to radium-223 dichloride (including evidence from non-authorised use that might impact the authorised use) in order to assess their potential impact on the benefit-risk balance of Xofigo in the authorised indication of the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

On 30 November 2017 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Xofigo and to issue a recommendation on whether the marketing authorisation of this product should be maintained, varied, suspended or revoked.

The current recommendation relates only to provisional measures recommended by the PRAC for radium-223 dichloride based on the preliminary data available at this time. These provisional measures are without prejudice to the outcome of the ongoing review under Article 20 of Regulation (EC) No 726/2004.

Overall summary of the scientific evaluation by the PRAC

Xofigo (radium Ra223 dichloride, also radium-223 herein) is a centrally authorised product indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

The PRAC considered preliminary data analyses from a randomized, placebo-controlled multicentre phase III study (15396/ERA-223) in chemotherapy-naïve patients with asymptomatic or mildly symptomatic castration resistant prostate cancer with bone metastases (CRPC). The PRAC also considered data from the pivotal clinical trial ALSYMPCA which supported the marketing authorisation of Xofigo, as well as data from other completed and ongoing studies which became available since the marketing authorisation.

The clinical efficacy of radium-223 dichloride in the authorised indication was established during the initial marketing authorisation application based on the assessment of data from one pivotal phase III study (15245/BC1-06, ALSYMPCA), in which an improved overall survival and delayed symptomatic skeletal events were observed.

Based on the available data, Study 15396 shows that in chemotherapy-naïve asymptomatic or mildly symptomatic patients with CRPC, radium-223 in combination with concurrent abiraterone acetate and prednisolone/prednisone decreases overall survival and increases the risk of fractures compared to placebo in combination with abiraterone acetate and prednisone/prednisolone. The PRAC concluded that the risks observed were unlikely to be due to bias.

Whilst the exact extent of use of radium-223 in combination with abiraterone acetate and prednisolone/prednisone in clinical practice is not known, interim data from an observational study (REASSURE) reported that 5% of patients were treated with this combination. In view of the seriousness of these results, the fact that they were observed in a patient population with earlier disease characteristics but partly overlapping with that described in the authorised indication, and considering that the mechanism behind the events observed remain largely unexplained at this stage, the PRAC considered that, as a provisional measure, the use of radium-223 in combination with abiraterone acetate and prednisone/prednisolone should be contraindicated. Healthcare professionals should be informed of the increased incidence of fractures and deaths among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone in Study ERA-223, and of the reduced incidence of fractures observed in both treatment arms with concurrent use of bisphosphonates or denosumab bone health agents.

Whilst at this stage it is not excluded that the concurrent administration of radium-223 + abiraterone + prednisolone/prednisone is critical to the subsequent increased risks of fractures and death, it cannot be excluded either that the risks observed could apply to other effective androgen receptor antagonists. Interim results of the REASSURE study report also a significant concomitant use with enzalutamide in clinical practice (22%). Considering current therapeutic options available for patients with symptomatic castration resistant prostate cancer with bone metastases, the PRAC considered that as a provisional measure, a warning that the safety and efficacy of Xofigo in combination with second-generation androgen receptor antagonists such as enzalutamide have not been established, should be included in the product information.

These recommendations should be reflected in the product information and communicated to healthcare professionals via a dedicated letter. These measures will be further reviewed as part of the ongoing Article 20 procedure.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, in particular regarding the need for provisional measures in accordance with Article 20(3) of Regulation (EC) No 726/2004 for Xofigo (radium Ra223 dichloride) and taking into account the grounds set out in Articles 116 of Directive 2001/83/EC.
- The PRAC reviewed the preliminary data analyses of Study ERA 223 that suggested an increased risk of fracture and mortality when radium Ra223 dichloride treatment, compared to placebo, is initiated concurrently with abiraterone acetate and prednisone/prednisolone treatment. The PRAC also considered other available data, including further data from the ALSYMPCA clinical trial submitted in support of the initial marketing authorisation, in relation to the potential impact of results of Study ERA 223 on the benefit-risk balance of radium Ra223 dichloride in its authorised indication.
- The PRAC noted that the use of radium Ra223 dichloride in Study ERA 223 was at earlier stages of the disease, albeit partially overlapping with that included in the authorised indication. The PRAC also noted that data available show that radium Ra223 dichloride is used to some extent in clinical practice in combination with anti-androgens such as abiraterone and enzalutamide.
- Further to the review of the preliminary analyses available, the underlying mechanism for the increased risks of fracture and mortality observed in ERA 233, and therefore the potential impact of these findings in the authorised indication, remain uncertain. Therefore and in view

of the seriousness of the events observed, the PRAC recommended provisional amendments to the product information to contraindicate the use of radium Ra223 dichloride in combination with abiraterone acetate and prednisone/prednisolone and inform on the results of Study ERA 223.

- In addition, in the absence of definite evidence that the results observed were specific to the combination with abiraterone acetate and prednisone/prednisolone, the PRAC considered that healthcare professionals and patients should be warned that the safety and efficacy of radium Ra223 dichloride in combination with second-generation androgen receptor antagonists including enzalutamide have not been established.

In view of the above, the Committee considers that the benefit-risk balance of Xofigo (radium Ra223 dichloride) remains favourable subject to the agreed provisional amendments to the product information. The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Xofigo (radium Ra223 dichloride).

This recommendation is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004.