Annex IV

Scientific conclusions

Scientific conclusions

Analyses of uncleaned preliminary data of a clinical trial evaluating Xofigo (radium Ra223 dichloride) in a patient population with asymptomatic or mildly symptomatic prostate cancer (ERA-223 [1]), 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 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, pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the Agency on whether the marketing authorisation of Xofigo (radium Ra223 dichloride) should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation by the PRAC

Xofigo (radium-223 dichloride) 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 interim 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 phase III clinical trial ALSYMPCA (15245/BC1-06) 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 in the authorised indication was established during the initial marketing authorisation application based on the assessment of data from one pivotal study (ALSYMPCA), in which an improved overall survival and delayed symptomatic skeletal events were observed. At the time of marketing authorisation, based on the data from that pivotal clinical trial, radium-223-related adverse events were considered manageable and of lower intensity than those associated with the use of cytostatic drugs also used in the target population.

The PRAC noted that ERA-223 included chemotherapy-naïve adults with castration-resistant prostate cancer, no known visceral metastases and of which 46% had mildly symptomatic bone metastases. These characteristics are consistent with the authorised indication. Based on the available data, it cannot be demonstrated that the adverse outcomes in ERA-223 are due to mechanism specific to the concurrent use with abiraterone acetate and prednisone/prednisolone. In line with the oncology scientific advisory group meeting (SAG) outcome, PRAC therefore considered that these findings are relevant for the authorised indication.

Considering all available data from clinical, non-clinical studies and the literature, the PRAC, concluded that the use of radium-223 is associated with an increased risk of fracture during and after treatment, in the authorised indication. This view was also shared by the SAG. The magnitude of this risk is however not fully elucidated since in all studies available, as also noted by the SAG, significant limitations were identified regarding data collection on fractures, including lack of systematic follow-up of risk of fracture and lack of intensive monitoring of skeletal health. It remains that in ERA-223 all fractures were to be reported for a longer period of time than in ALSYMPCA and bone/computed tomography (CT) scan were performed in the treatment phase.

[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)

Subgroup analyses in ERA-223 suggest that the use of bisphosphonates and denosumab ("bone health agents" [BHA]) reduced the risk of "symptomatic skeletal event-free survival" events, in particular symptomatic pathological fractures, the reduction was more pronounced in the radium-223 group. The use of these medicines also reduced the risk of all fractures in both treatment arms but did not eliminate the increased risk in the radium-223 arm compared to placebo arm. The results from stratified Cox models and logistic regression models for fracture for ALSYMPCA and ERA-223 are relatively consistent, indicating that use of BHAs is strongly associated with a decrease in fracture risk and the time to first fracture in the radium-223 arm, and in the placebo arm in ERA-223, but not in the placebo arm in ALSYMPCA. This indicates that the use of these medicines can minimize the risk of fractures associated with radium-223, including as single systemic cancer therapy.

In available imaging data the most common type of fracture was osteoporotic fractures and nearly all the patients with these fractures had osteoporosis at baseline. The finding that the majority of fractures occurred outside of metastases is of concern and indicates a substantial off-target effect of radium-223 in ERA-223. Data from a biodistribution study showed that in most instances the hot spots of radium-223 accumulation corresponded to tumour deposits; however they can also correspond to non-malignant disease e.g. degenerative bone disease. Xofigo is believed to accumulate at sites of high bone turnover such as sites of degenerative bone disease (osteoporosis) or recent (micro-)fracture, increasing the risk of fractures. In multivariate analyses in ERA-223, medical history of osteoporosis and lower number of metastases at baseline (<6 vs. ≥6) was significantly associated with increased risk of fracture in the radium-223 arm, but not the placebo arm. In addition, in ERA-223 patients with less than 6 bone metastases at baseline experienced more fractures and had a shorter time-to-first-fracture compared to those who had 6 or more bone metastases; this might be partly explained by baseline imbalance in the length of prior androgen deprivation therapy. In ALSYMPCA the incidence of fractures in patients with less than 6 bone metastases was approximately two-fold compared to the placebo group. In multivariate analyses the risk of fracture tended to be increased in patients with less than 6 bone metastases compared to patients with 6 or more bone metastases in the radium-223 arm. In conclusion, medical history of osteoporosis and lesser extent of disease at baseline seem to be key contributing factors for occurrence of fractures and time to first fracture in the radium-223 arm with both a history of osteoporosis and having fewer than 6 bone metastases being associated with an increased risk of fractures in *post-hoc* analyses.

Based on the aforementioned observations, the PRAC considered that prior to starting radium-223 treatment bone status should be assessed using for example scintigraphy and bone mineral density measurement as well as the baseline risk of fractures of patients, based on the known risk factors and those identified in this procedure (e.g. osteoporosis, less than 6 bone metastases, medication increasing fracture risk and low body mass index). Other factors such as concomitant use of steroids may further increase the risk of fracture. In view of the delayed risk of fractures observed, these two aspects should be closely monitored for at least 24 months after treatment initiation. In addition, preventive measures such as the use of bisphosphonates or denosumab should be considered before starting or resuming treatment with Xofigo. Further, in patients with a high baseline risk of fracture, the benefit of treatment should be carefully assessed to outweigh the risk.

The PRAC noted that in ERA-223, the proportion of patients who have died with non-bone progression (e.g. progression in lymph nodes or liver) was notably higher in the radium-223 arm compared to the placebo group (14.5% [57/392] vs. 7.4% [29/394]). In the overall population, an increased risk of radiological non-bone progression in the radium-223 group compared to the placebo group (HR 1.376; 95% CI [0.972, 1.948], p=0.07) was also observed, raising concerns that radium-223 promotes visceral and lymph node metastases. A similar trend was observed in ALSYMPCA, where in patients who died due to prostate cancer, the proportion of death due to prostate cancer-related non-skeletal metastasis was higher in the radium-223 arm than the placebo arm (38.1% vs. 27.3%). The PRAC noted concerns raised at time of the initial marketing authorisation that the incidence of non-prostate cancer-related death in the radium-223 group was lower compared to the placebo group, which could indicate health status

imbalance favouring the radium-223 group. Other concerns had been raised such as the absence of demonstration of direct anti-tumour effect and the potential impact of co-medication such a bisphosphonates. However, unlike some of the SAG experts, the PRAC considered that the results of ERA-223, did not affect the overall validity of the overall survival improvement observed in ALSYMPCA in the radium-223 group compared to the placebo group and noted that the overall survival benefit persisted after adjusting for major confounding factors. Further, whilst no direct anti-tumour effect had been demonstrated, as also noted at the time of authorisation, other endpoints were supportive of a benefit of radium-223. Less patients in the radium-223 group experienced skeletal-related events (SRE) and time to first skeletal-related event was clinically significantly longer with six months difference. All aspects of the composite endpoint SRE were referring to clinically relevant aspects and there was a consistent beneficial effect in three of four parameters of the composite endpoint in favour of radium-223, with external beam radiation therapy (EBRT) being the dominant component.

Therefore, whilst there are limitations to extrapolate the trend for increased mortality from ERA-223 to ALSYMPCA, but also difficulties in reconciling the adverse outcomes observed in ERA-223 with the favourable outcomes in ALSYMPCA, considering that patients in ERA-223 had less advanced metastatic CRPC, the available data raise concerns about the use of radium-223 in early lines of therapy for symptomatic patients.

In ALSYMPCA, patients were either post-docetaxel, unfit for docetaxel, unwilling to receive docetaxel or docetaxel was not available to them for other reason. Consequently, the chemotherapy-naïve patient population included in the ALSYMPCA trial was not well defined and the extent and characteristics of the different subpopulations is unknown. ERA-223 was exclusively conducted in chemotherapy-naïve patients, which adds further concern to treat chemotherapy-naïve metastatic prostate cancer patients with radium-223. Since the authorisation of radium-223, abiraterone and enzalutamide have been authorised for chemotherapy-naïve and post-docetaxel prostate cancer patients based on robust data showing OS benefit. Chemotherapy and to a certain extent abiraterone and enzalutamide are capable of targeting nodal and visceral metastasis. The mode of action of radium-223 is limited to the bone environment and a significant proportion of men with CRPC have soft-tissue (nodal and/or visceral) disease, some of which might remain undetected prior treatment initiation. Further, median alkaline phosphatase (ALP, an approximate measure of osteoblastic activity) of patients in the ALSYMPCA study was 211 U/L, which is relatively high. In example, median ALP was notably lower in a Phase III study investigating treatment benefit of enzalutamide in post-docetaxel patients (115 U/L) or abiraterone in chemotherapy-naïve patients (91 U/L). Therefore, other patient population including a post-docetaxel group of patients does not automatically replicate the type of patients enrolled in ALSYMPCA in terms of extent of disease.

Overall, the PRAC considered that Xofigo should only be used as monotherapy, or in combination with a luteinising hormone releasing hormone (LHRH) analogue, for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment. This view was supported to a certain extent by some SAG experts who considered radium-223 a useful ‘last-line’ option when no other available treatments are preferred and recommended the conduct of a randomised controlled trial in patients in progression after at least two prior lines of therapy for metastatic disease. Restricting radium-223 beyond third line of treatments was however not supported by the PRAC in view of the known safety issues with subsequent lines of chemotherapy regimens and as there is limited data on sequencing of therapy in this patient population. In addition, a number of published studies indicate cross-resistances of abiraterone and enzalutamide or docetaxel in the post-abiraterone setting.

Whilst a majority of patients in ALSYMPCA had received prior docetaxel therapy, data is lacking for the use of radium-223 after further lines of treatment. In addition, results of the two completed randomised controlled trials are not consistent in terms of overall survival. The PRAC, in line with the advice of some of the SAG experts, therefore recommended to impose as a condition to the marketing authorisation of

Xofigo the conduct of a randomised double-blind multicentre study, in order to further characterise the safety and efficacy, in particular the risk of fractures and the risk of formation of visceral and nodal metastases in the settings of the restricted indication. In addition, in order to obtain further data in a timely manner, in line with the SAG advice, the PRAC also recommended that the conduct of a non-interventional post-authorisation safety study is imposed to further characterise its safety.

As the dataset evolved during this procedure, it is noted that the statistically significant mortality imbalance observed in the interim analysis of ERA-223 at the time of the provisional measures (HR 1.347; 95% CI [1.047, 1.732] p=0.02) was no longer statistically significant in the analysis after the database lock on 8 June 2018 (HR 1.195; 95% CI [0.950, 1.505] p=0.128). However, this trend is still of concern. In addition, approximately three times as many patients experienced fractures in the radium-223 arm compared to the placebo arm. Abiraterone is known to increase the risk of fractures, as well as prednisone/prednisolone and a synergistic effect of the triple combination cannot be excluded. Observational data reported that radium-223 is used in clinical practice in combination with abiraterone (16% based on interim data from the observational study REASSURE). Overall, the PRAC considered that the contraindication introduced at the time of provisional measures for the use of radium-223 in combination with abiraterone and prednisone/prednisolone should be maintained.

Whilst mechanistically abiraterone could potentially have a more negative effect on bone health than androgen receptor antagonists, considering the known pharmacological effects of this class of medicines on bone, a further increased risk of fractures may also occur when radium-223 is combined with these medicinal products. The interim data from REASSURE also indicate concomitant use with enzalutamide (22%). Similarly as chemotherapy is authorised for the treatment of mCPRC in combination with prednisone/prednisolone also known to adversely affect bones, a further increased risk cannot be excluded. In addition, whilst a small proportion of patients received in a first-generation anti-androgen in the radium-223 treatment phase in ALSYMPCA, there are currently no data establishing the safety and efficacy of radium-223 in combination with cancer therapies other than LHRH analogues. The PRAC also noted the concerns of the SAG regarding combination with any other effective treatments (including chemotherapy) and the combination of radium-223 with any other cancer therapies should be avoided unless benefits and risks of the combination can be established. It was acknowledged that LHRH analogues can also adversely affect bone via reduction of bone mineral density, however on balance, LHRH are part of the gold standard treatment for metastatic prostate cancer. It is therefore considered critical that testosterone levels are maintained at castrate level in patients with mCRPC. Further, in ALSYMPCA, 83.9% of patients were administered LHRH analogues during treatment with radium-223. In conclusion, the PRAC recommended against the combination of radium-223 with other systemic cancer therapies other than LHRH analogues.

For most of the patients who experienced a fracture in ERA-223, it occurred after their final dose of radium-223. Therefore, it is likely that the risk of fractures with radium-223 persists beyond the last injection and may further increase in patients who subsequently receive abiraterone or other medicines that can also cause osteoporosis and fractures. There are no clinical data to support a recommendation on a washout period between the last injection of radium-223 and abiraterone, although in clinical trials a four-week washout period is currently recommended for radium-223 and subsequent therapy. The PRAC acknowledged the view of the SAG that sufficient washout periods, including of prior therapies, should be established based on pharmacodynamics and not only pharmacokinetics. In the absence of clinical data, the PRAC considered that healthcare professionals should be advised to allow for a treatment-free interval based on elimination half-lives, of at least 5 days after abiraterone before initiating treatment with radium-223 and of at least 30 days after the last dose of radium-223 before a subsequent systemic cancer treatment is administered.

The definition of mildly symptomatic bone metastases has evolved since ALSYMPCA was conducted. However, given that there are significant concern regarding overall survival and fracture risk in asymptomatic patients from ERA-223 trial and no substantial data from ALSYMPCA or other trials indicating a benefit of radium-223 in these patients, Xofigo is not authorised in this subpopulation and

the benefit-risk balance is regarded as negative. It is noted that a proportion of clinicians may however consider it appropriate to extrapolate the results of ALSYMPCA to certain asymptomatic patients with bone metastases (St. Gallen Advanced Prostate Cancer Consensus Conference (APCCC) in 2015). Consequently, the PRAC recommended to include a warning in the product information to emphasise that the use of Xofigo is not recommended in this patient population.

As noted above, patients with fewer than 6 bone metastases had an increased risk of fractures both in ERA-223 and in ALSYMPCA. Further, in ALSYMPCA a statistically significant overall survival benefit of treatment could not be demonstrated in the subgroups of patients with fewer than 6 bone metastases (HR for radium-223 to placebo 0.901; 95% CI [0.553 - 1.466]. Further, as noted at the time of initial marketing authorisation, in ALSYMPCA a better radium-223 effect was demonstrated in patients having total ALP ≥220 U/L and thus in those patients having a high osteoblastic activity and probably higher extent of disease. Indeed a statistically significant overall survival benefit of treatment could not be demonstrated either in the subgroup of patients with a baseline total ALP < 220 U/L (HR 0.823; 95% CI [0.633 - 1.068], p=0.142). Interim data from an observational study showed that amongst patients who used radium-223 after at least two lines of therapy 12% had < 6 bone metastases and the median ALP of this group was lower than that of the ALSYMPCA population (167 U/L compared with 211 U/L). Therefore, it was noted that the restricted indication does not clearly exclude treatment of patients a low level of osteoblastic bone metastases. Considering this possibility, in view of the newly identified risk of fracture, of the mechanism of action of radium-223 and the lower expected efficacy, the PRAC concluded that in patients with a low level of osteoblastic bone metastases radium-223 is not recommended.

Some of the SAG experts were of the view that radium-223 could be a useful option as monotherapy only in patients with highly symptomatic bone metastases. In ALSYMPCA, radium-223 significantly prolonged overall survival in the group of non-opioids users (HR = 0.70; 95% CI [0.52–0.93]; p = 0.013), however, there were baseline differences in favour of radium-223. As the classification for pain severity has evolved since conduct of ALSYMPCA, there are some uncertainties whether reviewed ALSYMPCA data adequately defines patients classified as mildly symptomatic. While there is an overlap with ERA-223 in the study population defined as mildly symptomatic, differences in term of previous chemotherapy and treatment combination during the study make it difficult to extrapolate the negative results of ERA-223 to the authorised population. The PRAC considered that in adults with CRPC and mildly symptomatic bone metastases the benefit of treatment should be carefully assessed to outweigh the risks considering that high osteoblastic activity is likely to be required for treatment benefit.

In ERA-223, the median overall survival was reduced by 8.6 months in the group of patients who received 5 or 6 doses of radium-223, compared to those who received 5 or 6 doses of placebo. In addition, a statistically significant increase in the risk of fractures with radium-223 compared to placebo was observed in the subgroup of patients who received ≥5 , but no statistical differences was reached in the subgroup who received less doses - the sample size in this latter group was however much smaller. The PRAC considered that whilst not allowing to question the benefit risk balance of the currently established posology, the hypothesis that dosing is one of the factors that may have contributed to the increased risk of fracture and mortality should be further investigated.

In view of the above the PRAC recommended that the conduct of a biodistribution study should be imposed as a condition to the marketing authorisation of Xofigo in order to further characterize correlation between the extent of the disease, the dose and the distribution of radium-223 in bone metastases versus sites of impaired bone health (e.g. osteoporosis) versus normal bone structure.

The PRAC concluded that the benefit-risk balance remained positive, provided that Xofigo (radium Ra223 dichloride) is only used as monotherapy or in combination with LHRH analogue for the treatment of adult patients with mCRPC, symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment and that changes are implemented in the product information to minimise the risk of fracture. In addition, as a condition to the marketing authorisation, the efficacy

and safety of radium-223 must be further characterised via the conduct of a randomised controlled trial, a non-interventional post-authorisation safety study and a biodistribution study.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Xofigo (radium Ra223 dichloride).
- The PRAC reviewed the preliminary data analyses of Study ERA-223 that showed an increased risk of fracture and a trend for an increased risk of mortality compared to placebo when radium-223 treatment was combined with abiraterone acetate and prednisone/prednisolone treatment. The PRAC also considered all other available data, including data from the ALSYMPCA clinical trial which supported the initial marketing authorisation, in relation to the potential impact of the results of Study ERA-223 on the benefit-risk balance of radium-223 in the authorised indication. The PRAC also considered the views expressed by the scientific advisory group on oncology.
- The PRAC noted that the use of radium-223 in ERA-223 took place in chemotherapy-naïve patients at earlier stages of the disease, albeit partially overlapping with that included in the authorised indication. Considering all available data, the PRAC concluded that radium-223 is associated with an increased risk of fracture, during treatment and for several months after the end of treatment.
- The PRAC considered that the results of ERA-223 added to the uncertainties regarding the extent of benefit noted in ALSYMPCA at the time of initial marketing authorisation, in particular in patients with a lower disease burden and on the potential for radium-223 to promote non-bone disease progression. The PRAC thus considered that measures are needed to minimise these risks including preventing the use of the product in similar settings to that of ERA-223.
- As a consequence, the PRAC recommended that the indication of radium-223 is restricted to use as monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue, for the treatment of adults patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment. The PRAC further considered that radium-223 should be contraindicated in combination with abiraterone acetate and prednisone/prednisolone.
- In addition, considering the increased risk of fracture and as an increase in mortality is possible, the PRAC recommends not to use radium-223 in patients with only asymptomatic bone metastases or in combination with other systemic active cancer therapies. Treatment-free intervals before and after treatment with radium-223 are recommended.
- In view of the increased risk of fracture, the uncertainties raised, and the absence of significant evidence that the benefits observed in ALSYMPCA apply to patients with a low level of osteoblastic bone metastases, the PRAC recommends not to use radium-223 in these patients, and, in patients with mildly symptomatic bone metastases, to use radium-223 only if the benefits are expected to outweigh the risks.
- Further, the PRAC considered that in order to minimise the risk of fracture, healthcare professionals should assess bone status and baseline risk of fracture for all patients prior to initiating radium-223 and monitor patients for at least 24 months. The use of bisphosphonates or denosumab should be considered. In patients at high risk of fracture, radium-223 should only be initiated if the expected benefits are considered to outweigh the risks associated with the treatment.

- Finally, the PRAC recommended imposing as conditions to the marketing authorisation of Xofigo the conduct of a randomised controlled clinical trial, a non-interventional post-authorisation safety study and a biodistribution study, in order to further characterise the safety and efficacy of radium-223, including the mechanisms responsible for the increased risk of fracture, and possible risk of increased mortality reported in ERA-223.

In view of the above, the Committee considers that the benefit-risk balance of Xofigo (radium Ra223 dichloride) remains favourable subject to the agreed conditions to the marketing authorisation, and taking into account the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Xofigo (radium Ra223 dichloride).

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of Xofigo (radium Ra223 dichloride) remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Xofigo (radium Ra223 dichloride).