13 March 2018
EMA/170170/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report on provisional measures

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

Invented name: Xofigo

INN/active substance: radium Ra223 dichloride

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

Note:

Assessment report as adopted by the PRAC with all information of a commercially confidential nature deleted.

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1. Information on the procedure

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 [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 (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 report 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.

2. Scientific discussion

2.1. Introduction

Radium-223 dichloride is an alpha particle-emitter with a half-life of 11.4 days. The six-stage decay of radium-223 to lead-207 occurs via short-lived daughters, and is accompanied by a number of alpha, beta and gamma emissions with different energies and emission probabilities. The fraction of energy emitted from radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5.0−7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01−1.27 MeV).

Radium-223 dichloride mimics calcium and, after systemic administration, selectively targets bone 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 deoxyribonucleic acid (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.

Xofigo is a radiopharmaceutical containing radium Ra223 dichloride (also radium-223 herein) as active substance. It is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases. Marketing authorisation was granted in the European Union (EU) on 13 November 2013. The dose regimen of radium-223 dichloride is an activity of 55 kBq per kg body weight, given at 4-week intervals for 6 injections.

[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)

Since the first marketing authorisation (United States [US], 15/05/13) until 30 November 2017, it is estimated that cumulatively, approximately 41,262 patients have been exposed to the marketed product worldwide, of which 15,251 patients are from EU member states. Cumulative exposure to radium-223 dichloride in clinical studies until 30 November 2017 is approximately 4,828 subjects (2,762 in on-going studies and 2,066 from completed studies).

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. However, bone marrow toxicity, including thrombocytopenia and neutropenia are recognised adverse drug reactions. In addition, a potential signal of a risk of fractures was raised by non-clinical data during the initial marketing authorisation application; the clinical relevance of these findings is unknown. Fractures have not been identified as a risk of treatment with radium-223 dichloride and therefore are not identified as a safety concern in the risk management plan (RMP). However, the summary of product characteristics (SmPC) for Xofigo specifies under warning and precautions that in patients with untreated imminent or established spinal cord compression, treatment with standard of care, as clinically indicated, should be completed before starting or resuming treatment with Xofigo and further, in patients with bone fractures, orthopaedic stabilisation of fractures should be performed before starting or resuming treatment with Xofigo.

On 17 November 2017, the EMA was notified by the marketing authorisation holder (MAH) that Study 15396 had been un-blinded early on the recommendation of the Independent Data Monitoring Committee (IDMC) because of significant imbalances in fractures and death between the two treatment groups. These initial data had been released prior to a survival sweep and data cleaning. Emerging analyses from Study 15396 (ERA-223) initially triggered a signal review (EPITT 19132), as an outcome of which, at the same time as this Article 20 procedure was started, the PRAC agreed on the wording of a “direct healthcare professional communication” (DHPC) together with a communication plan for relevant HCPs to be informed of the preliminary results available and be advised not to treat patients with radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone with metastatic castration-resistant prostate cancer.

Having assessed analyses submitted by the marketing authorisation holder in responses to the list of questions, the PRAC considered that provisional measures were necessary in order to protect public health while the review is ongoing.

2.2. Clinical aspects

The PRAC considered all data submitted by the MAH. This included updated interim analysis of Study 15396 (ERA-223) and data from the pivotal ALSYMPCA trial [2]. In addition the MAH provided available results from a number of completed and ongoing randomised and non-randomised clinical studies including, non-interventional studies, investigator-initiated studies and from publications. A summary of the most relevant information is included below.

2.2.1. Data related to the emerging findings on fractures and deaths

2.2.1.1. Study 15396 (ERA-223)

Study 15396 (ERA 223) is an on-going, randomised, double blind, phase III study, which started on 30 March 2014. Enrolment was completed in September 2016, the last patient last radium-223 dichloride injection was in February 2017 and primary completion as per protocol is anticipated to occur around March 2018.

[2] A Phase III Study of radium-223 dichloride in patients with symptomatic hormone refractory prostate cancer with skeletal metastases (ALSYMPCA)

The MAH has now provided updated analyses performed based on the uncleaned data as of 14 December 2017 after the survival sweep was completed. All death-related analyses included death events up to the cut-off date of 24 November 2017, which is the starting date of the survival sweep. Most of the additional death events occurred before the death cut-off date of 24 November 17. Any other analyses included all data up to 14 December 2017. Data cleaning activity and central radiological review of fractures, which had been initiated after the imbalance in incidence of fractures had become apparent, is still on-going. Additional analyses of clinical data including clinical response markers (e.g. prostate-specific antigen [PSA]/ alkaline phosphatase [ALP]), time to non-bone progression, treatment emergent adverse events leading to any treatment discontinuation/dose modifications, summary of all fractures for patients with exposure to denosumab/bisphosphonates, treatment duration of bone health agents (BHAs), and lab abnormalities are also still expected.

2.2.1.1.1. Patients

The study enrolled asymptomatic or mildly symptomatic, chemotherapy-naïve patients with bone predominant metastatic castrate-resistant prostate cancer (mCRPC). Asymptomatic was defined as a worst pain score (WPS) of 0 on the Brief Pain Inventory-Short Form Question #3 (worst pain in last 24 hours) and mildly symptomatic was defined as a WPS of 1-3; 46% of patients in the study were mildly symptomatic patients. Maintenance of testosterone to castrate levels (< 50 ng/dL) was required through medical (luteinizing hormone-releasing hormone [LHRH] analogues) or surgical castration.

2.2.1.1.2. Study design

Phase III, double-blind, randomized, placebo-controlled, parallel group study. The study period consists of screening/randomization 1:1, treatment period, active follow-up with clinic visits, active follow-up without clinic visits and long-term follow-up phases.

The treatment period consisted of two phases:

- Treatment with up to 6 cycles of intravenous (IV) administrations of radium-223 dichloride 55 kBq/kg body weight (Arm A) or placebo (Arm B), each separated by an interval of 4 weeks, plus abiraterone acetate 1000 mg every day plus prednisone/prednisolone 5 mg twice daily. Radium-223 dichloride/placebo treatment was started on the same day as the abiraterone/prednisone treatment and used concurrently.
- Ongoing treatment with abiraterone plus prednisone/prednisolone. After completion of treatment with radium-223 dichloride (Arm A) or placebo (Arm B), all randomized subjects will continue to receive abiraterone acetate 1000 mg every day plus prednisone/prednisolone 5 mg twice daily until an on-study symptomatic skeletal event (SSE) occurs (or other withdrawal criteria are met).

2.2.1.1.3. Results

Main study results are included below

Table 1. Fractures, symptomatic skeletal event free survival (SSE-FS) and deaths in Study 15396

	Arm A (Radium-223) Radium-223 + abiraterone + prednisone/prednisolone	**Arm B (placebo)** Placebo + abiraterone + prednisone/prednisolone
Fractures[1] (No of patients with≥1 fracture)	26.0% (102/392)	8.1% (32/394)

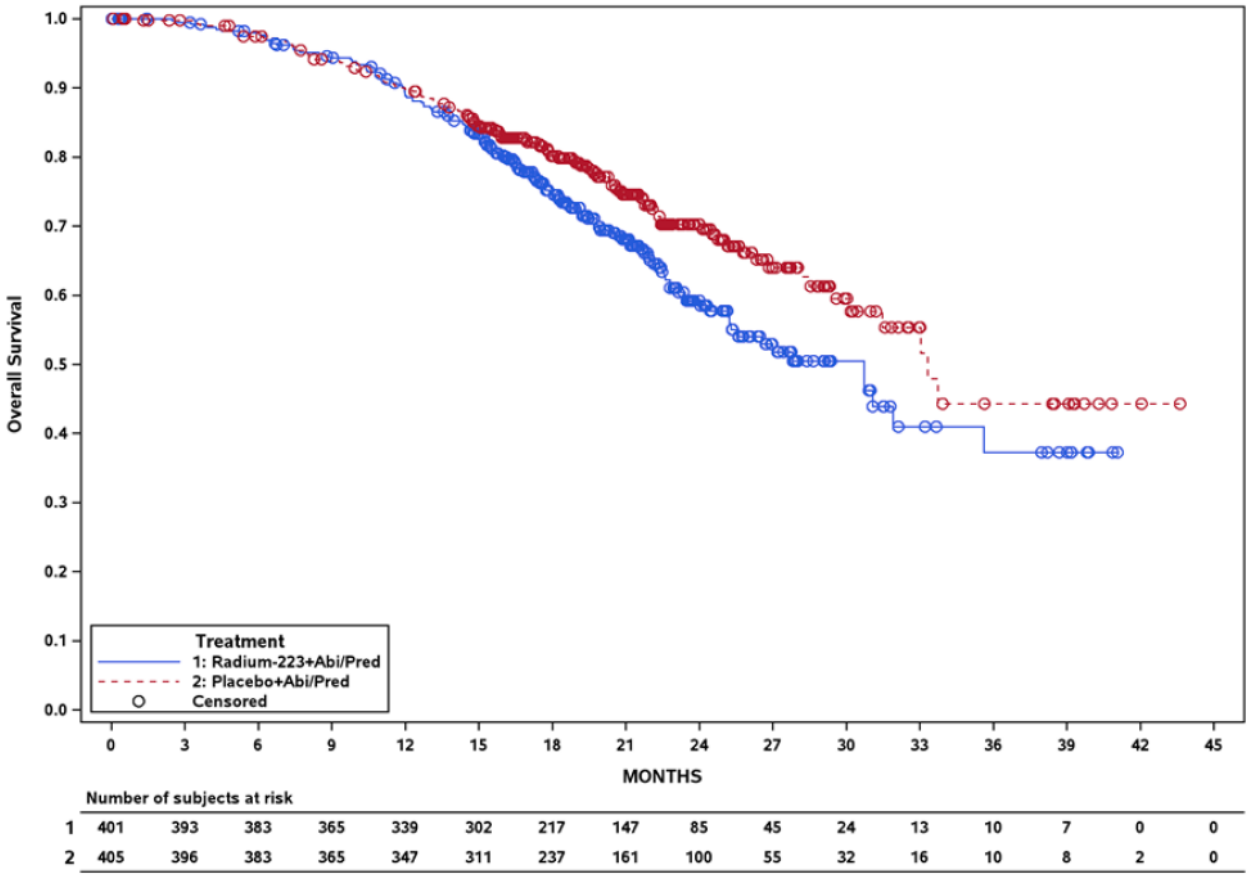
SSE-FS events[2] (No of patients with event)	43.4% (174/401)	39.8% (161/405)
Median (95% CIs) SSE-FS[2] **(months)**	22.6 (20.4, 29.3)	28.7 (21.8, 31.6)
Survival analysis[2]		
Deaths	34.7% (139/401)	27.4% (111/405)
P value	0.02	
HR (95% CIs)	1.347 (1.047, 1.732)	
Median OS (95% CIs) (months)	30.7 (25.2, 35.6)	33.3 (30.2, A)

SSE-FS = symptomatic skeletal event-free survival; OS = overall survival
[1]Based on safety analysis; [2]based on ITT population

2.2.1.1.3.1. Death

Median overall survival (OS) was reduced in the radium-223 plus abiraterone/prednisone treatment arm compared to the placebo arm (Table 1, Figure 1).

Figure 1. Kaplan-Meier curve for overall survival (ITT analysis)



Of the 136 deaths in the radium-223 group:

- 2 deaths occurred in the treatment phase, before or on the last dose date of radium-223 (+ 30 days)

- 19 deaths occurred in the treatment phase, before or on the last dose date of treatment with abiraterone/prednisone (+ 30 days)

- 115 deaths occurred after the last dose date of treatment with radium-223 and/or abiraterone acetate + prednisolone/prednisone (+30 days).

Death due to progressive disease was reported as the main reason for the imbalance in deaths observed between the treatment arms (Table 2). It is not known at this stage whether the deaths due to disease progression in the radium-223 group were due to bone progression or progression in soft tissue/visceral disease.

Table 2. Primary cause of death (safety analysis set)

	Radium-223 +Abi/Pred N=392 (100%)	Placebo +Abi/Pred N=394 (100%)
Number (%) of deaths	**136 (34.7%)**	**111 (28.2%)**
Primary cause of death		
Progressive disease	93 (23.7%)	76 (19.3%)
Adverse event associated with clinical disease progression[b]	13 (3.3%)	12 (3.0%)
Adverse event not associated with clinical disease progression[b]	12 (3.1%)	9 (2.3%)
Unknown	10 (2.6%)	7 (1.8%)
Other[c]	8 (2.0%)	7 (1.8%)

a: Any study treatment (radium-223 dichloride/placebo and/or abiraterone/prednisone)
b: Treatment-Emergent Grade 5 Adverse Events are presented in Table 2-3.

In the safety analysis set, most deaths in the radium-223 (97/136 [71%]) and placebo groups (99/111 [89%]) occurred without any prior fracture reported (Table 3).

Table 3. Relationship between all fractures, SSE fractures and deaths (safety analysis set)

	Ra223+Abi/Pred (n = 392) (=100%)	**Placebo+Abi/Pred (n = 394) (=100%)**	**Relative Risk (RR) / Risk difference (RD) (Ra223 vs. Plc)**
Number of deaths	**136 (34.7%)**	**111 (28.2%)**	**RD 6.5% RR 1.23**
Death without any prior fractures	97 (24.7%)	99 (25.1%)	RD -0,4% RR 0.98
Death with prior fractures	39 (9.9%)	12 (3.0%)	RD 6.9% RR 3.27
Death with prior SSE fractures	20 (5.1%)	8 (2.0%)	RD 3.1% RR 2.51
Death with prior non-SSE fractures	23 (5.9%)	4 (1.0%)	RD 4.9% RR 5.78

In both treatment groups, there were higher proportions of deaths in patients with higher extent of disease (> 20 lesions and Superscan) and higher ECOG score (Eastern Cooperative Oncology Group scale used to indicate how a patient's disease progresses and affects daily life) at baseline (Table 4).

2.2.1.1.3.2. Fractures

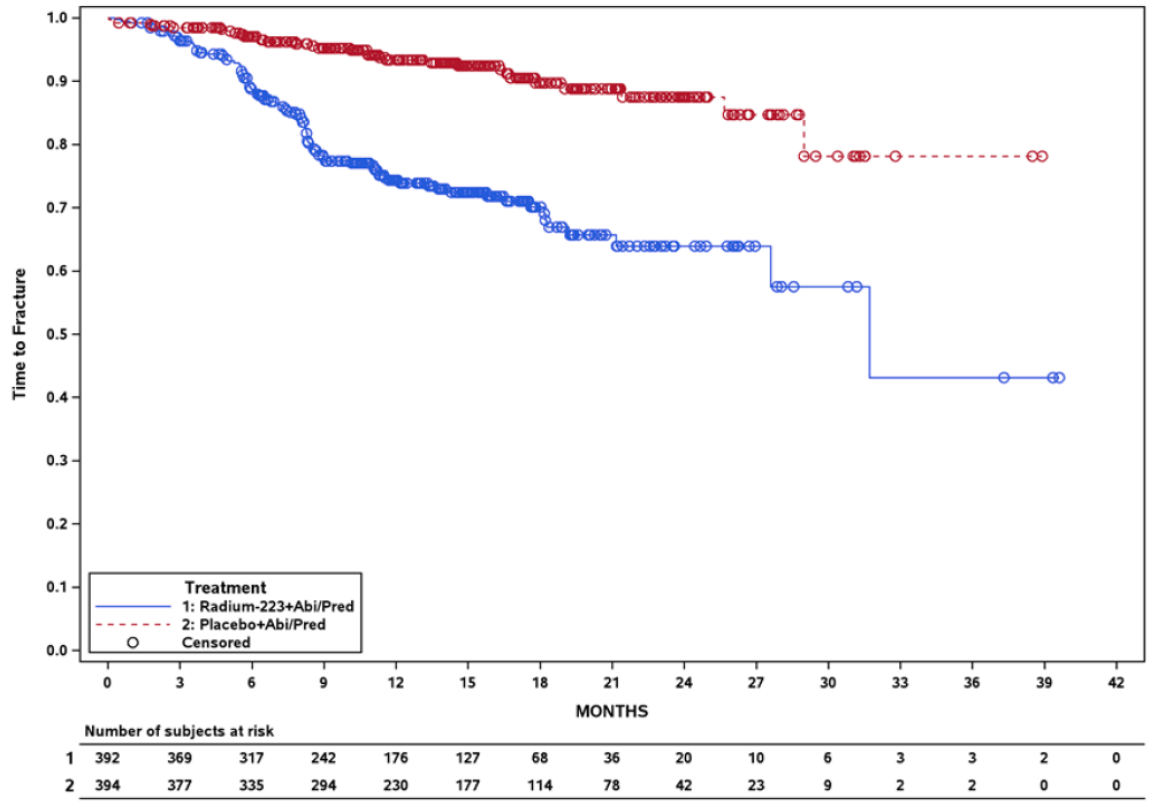
Baseline characteristics of patients with and without fractures are summarised in Table 4.

Table 4. Baseline characteristics of patients with and without fractures, Study 15396 (safety analysis set)

	Radium-223+Abi/Pred N=392 (100%)		Placebo+Abi/Pred N=394 (100%)	
	With fractures N = 102	Without fractures N = 290	With fractures N = 32	Without fractures N = 362
Extent of bone disease at baseline				
<6 metastases	50(49.0%)	83(28.6%)	10(31.3%)	126(34.8%)
6-20 metastases	27(26.5%)	143(49.3%)	16(50.0%)	158(43.6%)
>20 lesions but not a superscan	19(18.6%)	51(17.6%)	5(15.6%)	64(17.7%)
Superscan	6(5.9%)	13(4.5%)	1(3.1%)	13(3.6%)
Missing	0	0	0	1(0.3%)
ECOG performance status at baseline				
0	65(63.7%)	189(65.2%)	17(53.1%)	251(69.3%)
1-2	35(34.3%)	99(34.1%)	14(43.8%)	109(30.1%)
≥2	1(1.0%)	2(0.7%)	1(3.1%)	2(0.6%)
Missing	1(1.0%)	0	0	0
Medical history of osteoporosis				
Yes	9(8.8%)	13(4.5%)	2(6.3%)	14(3.9%)
No	93(91.2%)	277(95.5%)	30(93.8%)	348(96.1%)
Concurrent use of BHA				
Yes	20(19.6%)	136(46.9%)	8(25.0%)	160(44.2%)
No	82(80.4%)	154(53.1%)	24(75.0%)	202(55.8%)
Body weight, kg,				
Mean	82.9	81.6	81.6	82.1
SD	17.6	16.2	20.0	15.6
Min	42	51	52	45
Median	81.0	80.5	81.2	81.0
Max	155	151	134	130
Duration of prior ADT				
0	0	8(2.8%)	0	11(3.0%)
<12 Months	13(12.7%)	38(13.1%)	4(12.5%)	39(10.8%)
12 to <24 Months	20(19.6%)	70(24.1%)	5(15.6%)	77(21.3%)
>=24 Months	69(67.6%)	174(60.0%)	23(71.9%)	235(64.9%)
Duration of prior systemic glucocorticoids				
0	92(90.2%)	267(92.1%)	28(87.5%)	330(91.2%)
<12 Months	5(4.9%)	13(4.5%)	2(6.3%)	19(5.2%)
12 to <24 Months	2(2.0%)	3(1.0%)	2(6.3%)	5(1.4%)
>=24 Months	3(2.9%)	7(2.4%)	0	8(2.2%)
Prior SRE				
Yes	25(24.5%)	64(22.1%)	7(21.9%)	76(21.0%)
No	77(75.5%)	226(77.9%)	25(78.1%)	286(79.0%)

In the safety analysis set, a higher proportion of patients in the radium-223 group had at least 1 fracture than in the placebo group (102/392 [26.0%] vs 32/394 [8.1%]) (Table 1). The Kaplan-Meier figure of time to fracture is shown below (Figure 2).

Figure 2. Kaplan-Meier figure of time to first fracture



In the radium-223 group, of the 102 patients who had ≥1 fracture:

- 22 (21.5%) had a fracture in the treatment period, before or on the last radium-223 dose

- 69 (67.5%) had a fracture in the treatment period, after concurrent treatment with radium-223 dichloride plus abiraterone/prednisone and before the last dose of subsequent abiraterone/prednisone treatment.

- 11 patients (11%) had a fracture that was reported after the last study dose (radium-223 and/or abiraterone acetate/prednisolone).

Radiological review of all fractures is currently on-going. Data from the first batch including 80 scans from 54 patients suggest that fractures occurred both at sites of metastases and outside of bone metastases.

2.2.1.1.3.3. Symptomatic skeletal event-free survival

A summary of SSE-FS events by components ((1) an on-study SSE, which is defined as: a. the use of external beam radiotherapy (EBRT) to relieve skeletal symptoms, b. the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral), c. the occurrence of spinal cord compression, d. a tumour-related orthopaedic surgical intervention; or (2) death from any cause) indicate that the most notable differences between the two treatment arms are an increased incidence of symptomatic pathological fracture (9.7% vs 3.7%) and death (34.7% vs 27.4%) in the radium-223 group compared to the placebo group. There was a slightly lower frequency of spinal cord compression events in the radium-223 group compared to the placebo group.

2.2.1.1.3.4. Effect of bone health agents (BHAs)

Subgroup analyses for the effect of BHA (i.e. bisphosphonates or denosumab) use were conducted for death, SSE-FS and all fractures (Table 5 and Table 6).

Table 5. Death and SSE-FS events by exposure to BHAs

	Radium-223 +Abi/Pred N=401 (100%)		Placebo +Abi/Pred N=405 (100%)	
SSE-FS Event Category	**BHA (N= 155)**	**No BHA (N= 246)**	**BHA (N= 169)**	**No BHA (N= 236)**
Any events	**62 (40.0%)**	**122 (49.6%)**	**71 (42.0%)**	**98 (41.5%)**
Death	53 (34.2%)	86 (35.0%)	48 (28.4%)	63 (26.7%)
External Beam Radiotherapy	25 (16.1%)	65 (26.4%)	32 (18.9%)	52 (22.0%)
Spinal Cord Compression	6 (3.9%)	5 (2.0%)	5 (3.0%)	14 (5.9%)
Symptomatic Pathological Bone Fractures	2 (1.3%)	37 (15.0%)	4 (2.4%)	11 (4.7%)
Tumor-Related Orthopedic Surgical Intervention	1 (0.6%)	9 (3.7%)	2 (1.2%)	4 (1.7%)

BHA = bone health agent. BHAs include bisphosphonates (etidronic acid, clodronic acid, pamidronic acid, alendronic acid, tiludronic acid, Ibandronic acid, risedronic acid, and zoledronic acid) and denosumab.
Note: Patients with multiple types of SSE-FS events are counted in more than one category of events.

Table 6. Summary of all fractures by exposure to BHAs (safety analysis set).

	Radium-223 +Abi/Pred N=392 (100%)		Placebo +Abi/Pred N=394 (100%)	
	BHA (N= 156)	**No BHA (N= 236)**	**BHA (N= 168)**	**No BHA (N= 226)**
Number (%) of patients with at least one fracture				
n	20 (12.8%)	82 (34.7%)	8 (4.8%)	24 (10.6%)
After last dose[a] date	4 (2.6%)	7 (3.0%)	2 (1.2%)	3 (1.3%)
Before or on last dose[a] date	16 (10.3%)	75 (31.8%)	6 (3.6%)	21 (9.3%)
Before or on last Radium-223 dichloride/placebo dose date	5 (3.2%)	17 (7.2%)	3 (1.8%)	3 (1.3%)

a: Any study treatment (Radium-223 dichloride/placebo and/or abiraterone/prednisone

Source: Table 2-14, Annex A

2.2.1.2. Data from other randomised clinical studies

The MAH provided Kaplan-Meier curves for survival and fractures for all randomised controlled clinical trials for radium Ra223 dichloride ongoing or completed following the initial marketing authorisation application. These are listed in the below table.

Table 7. Randomized controlled clinical studies in CRPC with radium-223 dichloride ongoing or completed since original submission, plus ALSYMPCA (15245, BC1-06)

Study number	Phase	Protocol title	Number treated
15469 (BC1-10)	Phase 1/2	A Phase 1/2 study of safety and efficacy of radium-223 dichloride with docetaxel in patients with bone metastases from CRPC	63 (50 received radium-223 dichloride)
16507	Phase 2	A three-arm randomized open-label Phase II study of radium-223 dichloride 55 kBq/kg vs. 88 kBq/kg, and vs. 55 kBq/kg in an extended dosing schedule in subjects with CRPC metastatic to the bone	370
16544	Phase 2	A randomized open-label Phase IIa study evaluating quantified bone scan response following treatment with radium-223 dichloride alone or in combination with abiraterone acetate or enzalutamide in subjects with CRPC who have bone metastases	63
15245 (BC1-06)	Phase 3	ALSYMPCA-A double-blind, randomized, multiple dose, Phase 3, multicenter study of radium-223 dichloride solution for injection in the treatment of patients with symptomatic hormone-refractory prostate cancer with skeletal metastases	901 (624 received radium-223 dichloride)[#]

In two of the studies, 16544 and 15469, the sample sizes were small (63 patients treated in each study) and there was a high degree of censoring for the OS endpoint.

Study 16507 is a randomized, 3-arm, open-label Phase 2 study that evaluated 3 different doses. The proportion of patients with an SSE-bone fracture was increased in the high dose (9/130 [10.6%]) and extended dose (10/131 [10.9%]) groups compared to the standard dosing group, (1/130 [5.0%]).

The pivotal Phase III study, ALSYMPCA was a randomized (2:1), double blind, placebo controlled multinational study of radium-223 plus best standard of care (BSC) compared with placebo plus BSC in CRPC patients with symptomatic bone metastases. Analyses submitted to support the marketing authorisation application are presented and discussed further below (see section 2.2.3. and 2.2.4.). The incidence of all fractures was similar in the radium-223 and placebo arms (6.5% vs 6.6%).

2.2.1.3. Data from non-randomised clinical studies

Based on the ALSYMPCA trial, two clinical studies (Expanded Access Program) were conducted in order to provide access to radium-223 dichloride for patients with castrate resistant prostate cancer patients with bone metastases prior to reimbursement decisions by national health services. Study 15995

(NCT01516762 [3]) was conducted in the US, and Study 16216 (NCT01618370 [4]) was conducted outside of the US.

Several non-interventional clinical studies investigating the efficacy and/or safety of radium-223 dichloride are currently ongoing. Preliminary data from the global REASSURE study (5) and the PARABO study (6) conducted in Germany only are available. In addition, several Real-World (RW) datasets should provide information on current treatment patterns of radium-223 dichloride in real-life use: the Navigant study (7) and the FlatIron Database (8). However, results of the Navigant study and FlatIron RW database are not available yet.

If all patients from all studies are pooled, 449 out of 3449 (13.0%) patients received abiraterone acetate plus prednisone/prednisolone together with radium-223 dichloride. However the baseline characteristics of all patients in the above studies vary widely in terms of lines of treatment received before therapy with radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone. The use in combination in these studies refers to any overlap between the treatment of abiraterone acetate and prednisone/prednisolone and radium-223 regardless of timing of initiation. This is not identical to the study design of ERA-223 where both medicinal products were started at the same time. In the REASSURE study 3 out of 73 patients (4.1%) started radium-223 dichloride within the first month of abiraterone acetate plus prednisone/prednisolone, which would correspond to the situation of the ERA-223 trial. The interim data from REASSURE also indicate significant concomitant use with the anti-androgen enzalutamide (22%). Interim analysis from this study also shows concomitant use of corticosteroids and radium-223 in 21% (124/583) of patients.

In Study 15995 (US Early Access Program), 184 patients received at least one dose of radium-223. Concurrent abiraterone was administered to 25 of 184 (14%) patients (Sartor, 2017). Patients had symptomatic, progressive, bone-predominant mCRPC with ≥ 2 bone metastases on imaging with no lung, liver, or brain metastases. The incidence of deaths was lower in the subgroup with concurrent abiraterone compared to the total population (4/25 [16%] vs 50/184 [27%]). There were few pathological fractures (4 in the total population, including 1 in the subgroup with concurrent abiraterone) and only 1.1% of patients had a non-pathological fracture during the treatment period.

In Study 16216 (international Early Access Program) of 708 patients who received radium-223, 119 (17%) received concomitant abiraterone (Saad, 2016). Patient eligibility criteria were similar to the ALSYMPCA trial, although unlike ALSYMPCA, asymptomatic patients were eligible for this study. The incidence of deaths was lower in the subgroup with concurrent abiraterone compared to the total population (31/119 [26%]) vs 224/708 [32%]).

2.2.2. Discussion on the emerging findings related to fractures and deaths

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

[3] Sartor O, N. J. V., et al. for the US Expanded Access Program Investigators (2017). "Radium-223 Safety, Efficacy, and Concurrent Use With Abiraterone or Enzalutamide: First US Experience From an Expanded Access Program." The Oncologist in press.
[4] Saad, F., J. Carles, et al. (2016). "Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial." Lancet Oncol 17(9): 1306-1316.
[5] Observational study for the evaluation of long-term safety of radium-223 used for the treatment of metastatic castration resistant prostate cancer (REASSURE, NCT02141438)
[6] Pain evaluation in radium-223 (Xofigo) treated mCRPC patients with bone metastases - a non-interventional study in nuclear medicine centers (PARABO, NCT02398526)
[7] An anonymised retrospective chart review study of clinical parameters and patient determinants that drive physician decision making for treatment selection including radium-223 dichloride for patients with mCRPC
[8] US database of patients with a confirmed diagnosis of metastatic prostate cancer who have been treated with radium-223 dichloride

placebo in combination with abiraterone acetate and prednisone/prednisolone. Important prognostic factors were balanced between the two groups at baseline. Also, the use of BHAs was balanced at baseline (~ 40%) and these medicines could not be started during the study. Therefore, the observed results are unlikely to be due to bias. In addition, the median OS in the control group in Study 15396 (33.3 months) is similar to the median OS in the abiraterone + prednisone group in COU-AA-302 (34.7 months; abiraterone product information) (9), adding to the validity of the results. While a similar signal was not seen in other studies where radium-223 was administered in combination with concurrent abiraterone acetate and prednisolone/prednisone, only a small proportion of patients in these studies started the combination at the same time, as was the case in ERA-223. Further, these studies have important limitations either in term of sample size and censoring for the OS endpoint or the absence of control group, the absence of random assignment or blinding, small subgroup of patients with concomitant abiraterone acetate, short follow up and the potential for selection bias i.e. patients with better prognosis being selected for combination treatment.

The higher risk of death in the radium-223 group in study 15396 appears to be driven by a higher incidence of disease progression as a cause of death. However it is not excluded at this stage that fractures may be an important contributory factor to the increased risk of death. Further other unknown factors may also have contributed. Subgroup analysis, which should be interpreted with caution, suggests that bone health agents (BHAs) did not mitigate the increased risk of death in the radium-223 group; further analyses are required to try to establish if this is correct.

For the majority of patients who experienced a fracture, the fracture occurred after their final dose of radium-223. This delayed occurrence of fractures has been observed with post-radiation therapy fractures, which can occur several months after radiation is administered (Shimoyama, 2017 [10]). Data from a *post hoc* subgroup analysis, which should therefore be interpreted with caution, suggest that the use of BHA was associated with a reduced risk of fractures (symptomatic pathological fractures and non-SSE fractures) in both treatment groups of study ERA-223. Based on this *post hoc* analysis the use of BHA seems to also reduce the risk of the SSE-FS events external beam radiotherapy and to a lesser extent tumour-related orthopaedic surgical intervention, but not spinal cord compression and death in the radium-223 treatment arm. Further, the use of BHA appeared to eliminate the increased risk of symptomatic pathological fractures in the radium-223 group compared to the placebo group. No clear predictive baseline characteristic for fractures has been identified so far, except for concurrent use of BHA which appeared to reduce the risk of fractures in both arms. Nonetheless, another *post hoc*, subgroup analysis, suggest that in the radium-223 group, the risk of fracture appears to be higher in patients with <6 bone metastases compared to patients with ≥6 bone metastases.

Fractures (other than pathological fractures) are a recognised risk of treatment with abiraterone acetate (Zytiga SmPC). Unlike other anti-androgens, abiraterone blocks the synthesis of androgens and subsequently reduces oestrogen levels, thereby inhibiting osteoblasts and increasing osteoclast net activity. An abiraterone study, COU-301, in a post-docetaxel metastatic CRPC population, showed that the incidence of pathological fractures was higher in the abiraterone acetate + prednisone group than the placebo + prednisone group (15.3% vs 6.2%). However, this increase in the risk of pathological fractures should be interpreted with caution. BHAs were allowed to be initiated during the study in case of new skeletal event or bone progression, therefore, imbalances in the use of BHAs may have confounded the results (Logothetis, 2012 [11]). Furthermore, although prednisone (5 mg twice a day)

[9] NCT00887198: Abiraterone acetate in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer, Zytiga EPAR.
[10] Shimoyama T, Katagiri H, Harada H et al. Fracture after radiation therapy for femoral metastasis: incidence, timing and clinical features. J Radiat Res. 2017;58:661-668.
[11] Logothetis CJ, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain

was administered in both arms of the study, the median duration of treatment in the abiraterone group was twice that of the placebo group (8 cycles vs. 4 cycles) (Zytiga EPAR, Procedure No.: EMEA/H/C/002321). At this stage it is not excluded that the concurrent administration of radium-223 + abiraterone + prednisolone/prednisone is critical to the subsequent increased risk of fractures observed in study ERA-223.

Fractures are also a known risk for second-generation androgen receptor antagonists such as enzalutamide (Xtandi SmPC). The on-going PEACE-3 trial, which is comparing radium-223 in combination with enzalutamide in asymptomatic or mildly symptomatic CRPC patients, has not raised any signals regarding fractures and death; however, there are only 50 evaluable patients, therefore no conclusion can be made at this stage. The study aims to enrol 560 patients and the estimated study completion date is April 2021 (12).

Fractures are furthermore a known risk with first-generation androgen receptor antagonists such as flutamide, especially when combined with LHRH analogues (flutamide SmPC). About 15% of patients in the radium-223 group in the pivotal study, ALSYMPCA, received concomitant first-generation androgen receptor antagonists in the treatment phase. While it cannot be excluded that the risk of fractures observed when radium-223 is combined concurrently with abiraterone acetate also extends to other androgen receptor antagonists, in view of the population in which radium-223 is currently authorised, it is not expected that it would be administered as part of combination therapy with first-generation androgen receptor antagonists in clinical practice.

Based on data from the observational study REASSURE, it appears that radium-223 is combined to some extent with other anti-androgens in clinical practice, notably abiraterone and enzalutamide.

2.2.3. Data on efficacy in the authorised indication

The clinical efficacy of radium-223 dichloride in the authorised indication had been established during the initial marketing authorisation application based on the assessment of data from one pivotal Phase III study (15245/BC1-06, ALSYMPCA).

The study was conducted in castration-resistant prostate cancer patients with symptomatic bone metastases. Symptomatic was defined as either regular (not occasional) use of analgesic medication for cancer related bone pain (≥ level 1; WHO ladder for cancer pain), or treatment with EBRT for bone pain (the EBRT should have been within previous 12 weeks before randomisation). The study included 41.9% of mildly symptomatic patients.

Subjects were randomized 2:1 to receive either radium-223 dichloride or placebo. Other treatments for prostate cancer, best standard of care (BSC), could be used in accordance with routine clinical practice, at the discretion of the Investigator. BSC included local external beam radiotherapy, bisphosphonates, corticosteroids, oestrogens, estramustine, ketoconazole or anti-androgens (bicalutamide, flutamide and nilutamide). 40% of patients were receiving bone health agents at baseline and up to 51% in the follow-up period. Approximately 15% of patients received a first-generation anti-androgen (e.g. bicalutamide) in the treatment phase and approximately 40% to 60% received concomitant corticosteroids at different stages of the study. When this study was being conducted, abiraterone acetate and enzalutamide were not authorised.

The results of both the interim and updated analysis had shown that overall survival was significantly longer in patients treated with radium-223 plus BSC compared to patients treated with placebo plus BSC (Table 8 and Figure 3).

control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol 2012;13(12):1210–7.

[12] https://clinicaltrials.gov/ct2/show/NCT02194842, accessed 21/02/18

Table 8. Survival results from the phase III ALSYMPCA study

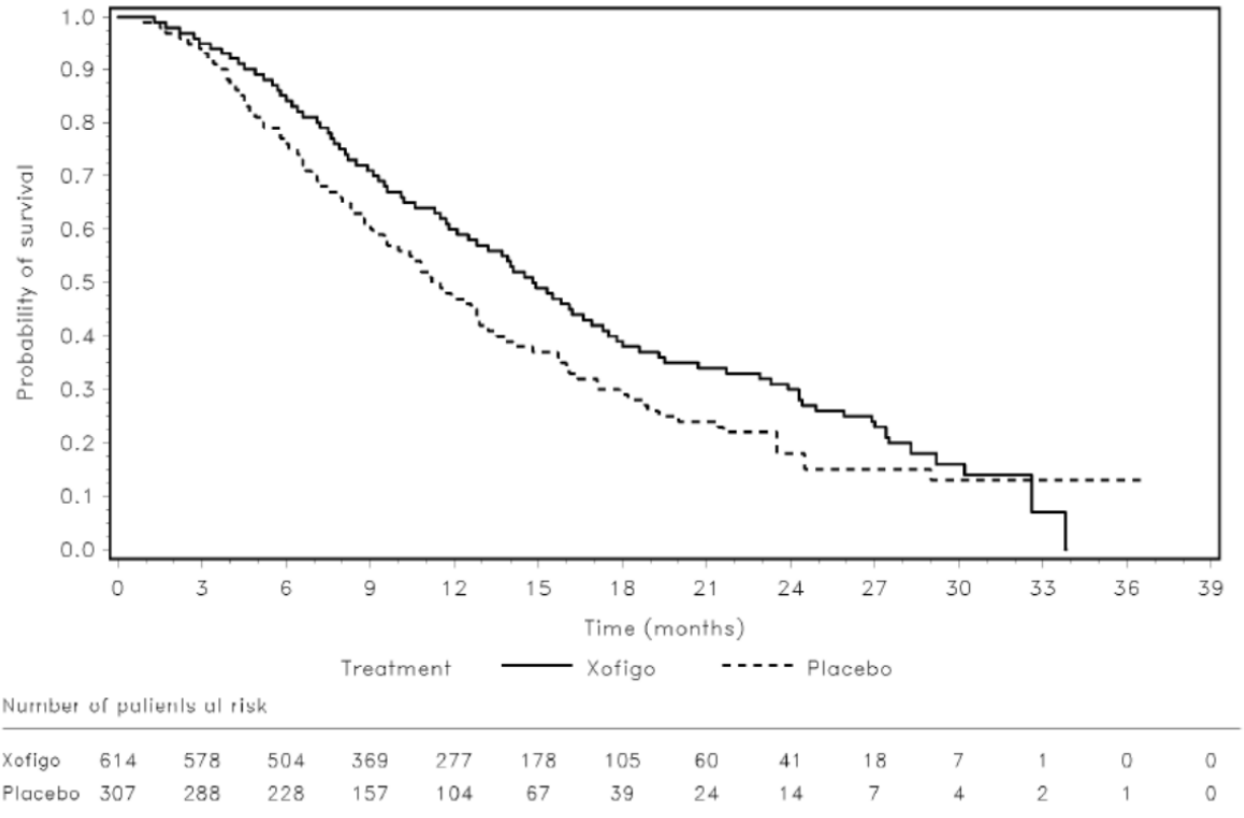
	Xofigo	Placebo
Interim analysis	N = 541	N = 268
Number (%) of deaths	191 (35.3%)	123 (45.9%)
Median overall survival (months) (95% CI)	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)
Hazard ratio[b] (95% CI)	0.695 (0.552 – 0.875)	
p-value[a] (2-sided)	0.00185	
Updated analysis	N = 614	N = 307
Number (%) of deaths	333 (54.2%)	195 (63.5%)
Median overall survival (months) (95% CI)	14.9 (13.9 – 16.1)	11.3 (10.4 – 12.8)
Hazard ratio[b] (95% CI)	0.695 (0.581 – 0.832)	

CI = confidence interval

[a] The Phase 3 study ALSYMPCA was stopped for efficacy after the interim analysis. As the updated analysis is provided for descriptive purposes only, a p-value is not provided.

[b] Hazard ratio (Xofigo over placebo) < 1 favours Xofigo.

Figure 3. Kaplan-Meier overall survival curves (updated analysis), ALSYMPCA study



The results of the interim analysis and the updated analysis had also shown a significant improvement in all main secondary endpoints in the radium-223 arm compared to the placebo arm, although the effect of delaying median PSA progression (median 0.2 months) was small (Table 9).

Table 9. Secondary efficacy endpoints from ALSYMPCA study (interim analysis)

			Incidence [no. (%) of patients]		Time-to-event analysis (95% CI) [median no. of months]			
			Xofigo N = 541	Placebo N = 268	Xofigo N = 541	Placebo N = 268	Hazard ratio < 1 favours Xofigo	p-value
Symptomatic skeletal event (SSE)	SSE composite endpoint [a]		132 (24.4%)	82 (30.6%)	13.5 (12.2–19.6)	8.4 (7.2 – NE)[b]	0.610 (0.461 – 0.807)	0.00046
	SSE components	External beam radiation for pain relief	122 (22.6%)	72 (26.9%)	17.0 (12.9–NE)	10.8 (7.9 – NE)	0.649 (0.483 – 0.871)	0.00375
		Spinal cord compression	17 (3.1%)	16 (6.0%)	NE	NE	0.443 (0.223 – 0.877)	0.01647
		Surgical intervention	9 (1.7%)	5 (1.9%)	NE	NE	0.801 (0.267 – 2.398)	0.69041
		Bone fractures	20 (3.7%)	18 (6.7%)	NE	NE	0.450 (0.236 – 0.856)	0.01255
Total ALP progression [c]			79 (14.6%)	116 (43.3%)	NE	3.7 (3.5 – 4.1)	0.162 (0.120 – 0.220)	< 0.00001
PSA progression [d]			288 (53.2%)	141 (52.6%)	3.6 (3.5 – 3.7)	3.4 (3.3 – 3.5)	0.671 (0.546 – 0.826)	0.00015

ALP = alkaline phosphatase; CI = confidence interval; NE = not estimable; PSA = prostate-specific antigen; SSE = symptomatic skeletal event

a Defined as occurrence of any of the following: external beam radiotherapy to relieve pain, or pathologic fracture, or spinal cord compression, or tumor-related orthopedic surgical intervention.

b not estimable owing to insufficient events after the median

c Defined as ≥ 25% increase compared to baseline/nadir.

d Defined as a ≥ 25% increase and an increase in absolute value of ≥ 2 ng/mL compared to baseline/nadir.

2.2.4. Discussion on efficacy in the authorised indication

In the single pivotal Phase III, placebo-controlled study in symptomatic patients with bone metastases from CRPC without visceral metastases, overall survival was longer in the radium-223 group compared to the placebo group by 2.8 months, based on the pre-specified interim analysis (HR 0.695, 95% CI 0.552-0.875, p=0.00185). The OS benefit persisted after correcting for baseline imbalances. Also, treatment of patients with radium-223 delayed the composite endpoint symptomatic skeletal events compared to placebo (median 13.5 months vs 8.4 months). At the time of authorisation, several uncertainties about the benefits of radium-223 dichloride were recognised, including but not limited to the absence of demonstration of a direct anti-tumour effect and to the potential impact of co-medication (e.g. bisphosphonates) on skeletal-related events.

The PRAC noted that radium-223 was an add-on to BSC in the pivotal clinical trial ALSYMPCA. However, several new medicinal products (e.g. abiraterone, enzalutamide) have been authorised for metastatic CRPC in the meantime, therefore it is difficult to put the beneficial effects of a bone-specific agent into context with current treatment standards. The PRAC also noted that overall survival analysis (including Kaplan-Meier graph) for the end of the follow-up period (database lock 10 October 2014) should be provided by the MAH.

3. Benefit-risk balance

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 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.

4. Risk management

4.1. Risk minimisation activities

4.1.1. Amendments to the product information

The PRAC considered that provisional routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risks of fractures and death associated with the use of radium-223 dichloride treatment initiated concurrently with abiraterone acetate and prednisone/prednisolone treatment. These changes include amendments to sections 4.3, 4.4, and 5.1 of the SmPC.

The PRAC considered that radium-223 dichloride should be contraindicated in combination with abiraterone acetate and prednisone/prednisolone

Further warnings and precautions of use relating to the risks of fracture and death among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone were also included together with important information that the safety and efficacy of combination with second-generation androgen receptor antagonists (e.g. enzalutamide) have not been established.

The Package Leaflet was amended accordingly.

4.1.2. Direct Healthcare Professional Communications/Communication plan

The PRAC adopted the wording of a Direct Healthcare Professional Communication (DHPC) to inform healthcare professionals of the recommended temporary contraindication and warnings regarding radium-223 dichloride.

5. Grounds for 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.