HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
2 April 2014

XOFIGO 1000 kBq/ml solution for injection
1 glass vial of 6 ml (CIP: 34009 585 762 7 0)

Applicant: BAYER HEALTHCARE SAS

INN	Radium-223 (Ra-223) dichloride
ATC Code (2013)	V10XX03 (Various therapeutic radiopharmaceuticals)
Reason for the request	**Inclusion**
List concerned	**Hospital use (French Public Health Code L.5123 2)**
Indications concerned	**"XOFIGO is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.»**

Actual Benefit	**The actual benefit of XOFIGO in the indication of treatment of castration-resistant prostate cancer, with symptomatic bone metastases and no known visceral metastases is substantial.**
Improvement in Actual Benefit	**XOFIGO provides a minor improvement in actual benefit (IAB IV) compared with a placebo in the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.**
Therapeutic Use	**XOFIGO represents a new therapeutic option in patients with castration-resistant prostate cancer, symptomatic bone metastases and no visceral or lymphatic involvement (malignant lymphadenopathy exceeding 3 cm). In the absence of data, its place in the chronological sequence compared with abiraterone acetate in patients presenting only bone metastases is unclear.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	13 November 2013 (centralised procedure) Previous temporary authorisation for use by a named patient [ATU nominative in French]
Prescribing and dispensing conditions /special status	List I Medicinal product reserved for hospital use. Medicine requiring special monitoring during treatment

ATC Classification	2013	
	V	Various
	V10	Therapeutic radiopharmaceuticals
	V10X	Other therapeutic radiopharmaceuticals
	V10XX	Various therapeutic radiopharmaceuticals
	V10XX03	radium (223Ra) dichloride

02 BACKGROUND

Assessment of the application for inclusion of the XOFIGO proprietary medicinal products 1000 kBq/ml solution for injection on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

XOFIGO is a radiopharmaceutical medicinal product containing a radioactive substance, radium-223 dichloride. Its active moiety mimics calcium and selectively targets bone and more specifically areas of bone metastases by forming complexes with the bone mineral hydroxyapatite.

03 THERAPEUTIC INDICATION

"XOFIGO is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases."

04 DOSAGE

"XOFIGO should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section 6.6 of the SPC) and after evaluation of the patient by a qualified physician.

Dosage
The dose regimen of XOFIGO is an activity of 50 kBq per kg body weight, given at 4 week intervals for 6 injections.

Safety and efficacy beyond 6 injections with XOFIGO have not been studied.

For details on the calculation of the volume to be administered see section 12 of the SPC.

Elderly patients
No overall differences in safety or efficacy were observed between elderly (aged ≥ 65 years) and younger patients (aged < 65 years) in the phase III study.

No dose adjustment is considered necessary in elderly patients.

Patients with hepatic impairment
Safety and efficacy of XOFIGO have not been studied in patients with hepatic impairment.
Since radium-223 is neither metabolised by the liver nor eliminated via the bile, hepatic impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.
No dose adjustment is considered necessary in patients with hepatic impairment.

Patients with renal impairment
In the phase III clinical study, no relevant differences in safety or efficacy were observed between patients with mild renal impairment (creatinine clearance [CLCR]: 50 to 80 ml/min) and normal renal function. Limited data are available on patients with moderate (CLCR: 30 to 50 ml/min) renal impairment. No data are available on patients with severe (CLCR < 30 ml/min) renal impairment or end-stage renal disease.
However, since excretion in urine is minimal and the major route of elimination is via the faeces, renal impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.
No dose adjustment is considered necessary in patients with renal impairment.

Method of administration
XOFIGO is for intravenous use. It must be administered by slow injection (generally up to 1 minute). The intravenous access line or cannula must be flushed with isotonic sodium chloride 9 mg/ml (0.9%) solution for injection before and after injection of XOFIGO. "

05 THERAPEUTIC NEED

Castration-resistant prostate cancer (CRPC) corresponds to the advanced stage of the metastatic disease. It is defined as biological and clinical progressive relapse despite effective castration. It generally occurs within 18 to 24 months after the initiation of androgen deprivation therapy in the metastatic patient.[1]
CRPC is a very heterogeneous disease; the median survival of patients is very different. However, at the metastatic stage, the median survival does not exceed 18 months and it is 9 to 12 months in cases of extensive metastases.
Around 50% of prostate cancer patients with bone metastases die within 30 months and 80% within 5 years. The first stages of castration-resistant prostate cancer (CRPC) with bone metastases are associated with significant pain (35% of patients) and an elevated level of prostate-specific antigen (PSA) in 90% of cases.[2]
Bone metastases result in numerous complications. Depending on their localisation and spinal cord involvement, they can be responsible for significant morbidity, in particular bone pain, fractures, spinal cord compression or haematological complications linked to bone marrow invasion. As soon as they become symptomatic, the bone metastases very clearly affect the patients' quality of life. The pain is often intense and requires use of opioid analgesics or external beam radiation therapy.
Recently, abiraterone acetate was granted MA in the treatment of patients with metastatic prostate cancer who are mildly symptomatic (most intense pain score experienced during the previous 24 hours < 3 on the VAS scale from 0 to 10), after failure of androgen deprivation therapy and in whom chemotherapy is not yet clinically indicated.

[1] Salomon L, Azria D, Bastide C et col. Recommandations en onco-urologie 2010 : cancer de la prostate. Progrès en Urologie 2010 ; 20(suppl.4) : S217-S252.
[2] XOFIGO EPAR, p8.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

A/ Radiopharmaceutical medicinal products

Two radioisotope medicinal products are indicated in bone metastases from prostate cancer, limited to analgesic treatment:

- METASTRON (Strontium-^{89} chloride) MA on 24 March 1993
- QUADRAMET 1.3 GBq/ml, solution for injection (Samarium ^{153}Sm) linked to a bisphosphonate)

It should be noted that the effect of these treatments on overall survival has not been evaluated.

NAME (INN) *Company*	Same TC* Yes/No	Indication	Marketing Authorisation	Date of Opinion
METASTRON (Strontium-^{89} chloride) GE Healthcare SA	Yes	"METASTRON is indicated as an adjunct to or as an alternative to external beam radiation therapy for the palliation of pain from bone metastases secondary to prostatic cancer at the stage of hormone therapy failure. The presence of bone metastases which take up technetium [99mTc]-labelled bisphosphonates should be confirmed prior to METASTRON injection. "	24/03/1993	NA**
QUADRAMET 1.3 GBq/ml solution for injection CIS BIO INTERNATIONAL	Yes	"QUADRAMET is indicated for the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases which take up technetium [^{99m}Tc]-labelled bisphosphonates on bone scan. "	05/02/1998	NA**

*TC: *Therapeutic category
**Not applicable: MA before the decree on 27 October 1999 regulating the rules of access to reimbursement

B/ Other medicinal products

Abiraterone acetate (ZYTIGA), in combination with prednisone or prednisolone, also has an indication in the same context, i.e. patients with metastatic prostate cancer limited to the bones who are mildly symptomatic (most intense pain score experienced during the previous 24 hours < 3 on the VAS scale from 0 to 10), after failure of androgen deprivation therapy and in whom chemotherapy is not yet clinically indicated.

06.2 Other health technologies

There are no non-medicinal treatment alternatives.

◗ Conclusion

METASTRON and QUADRAMET could be considered as clinically relevant isotope comparators of XOFIGO only for the analgesic effect on bone metastases. The effect on survival has not been investigated.

ZYTIGA can be considered as a relevant comparator at this stage of treatment.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
United States	YES (15/05/2013)	"XOFIGO is an alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. " .
Europe	In progress	

08 ANALYSIS OF AVAILABLE DATA

The submitted file includes the results from a pivotal study, the ALSYMPCA study (study 15245/BC1-06), described below.

08.1 Efficacy

8.1.1 ALSYMPCA study.[3,4]

A double-blind, randomised phase III study comparing the efficacy and safety of XOFIGO (radium dichloride) versus a placebo, associated with an optimal standard of care chosen by the investigator (including external beam radiation therapy, bisphosphonates, corticosteroids, oestrogens, antiandrogens, estramustine or ketoconazole) in patients with castration-resistant prostate cancer with symptomatic bone metastases. The presence of visceral metastases or malignant lymphadenopathy exceeding 3 cm is a non-inclusion criterion for the study.
The patients were randomised according to a 2:1 design to be treated with an IV bolus of radium-223 dichloride at a dose of 50 kBq/kg or a placebo, in combination, if necessary, with the best standard of care.
The patients received six administrations of the study treatment (radium-223 dichloride or placebo) with an injection every 4 weeks, at a dose of 50 kBq/kg.

The primary efficacy endpoint was overall survival, defined as the time between the date of randomisation and that of death from any cause.
The patients still alive on the date of analysis or lost to view were redacted on the date of last available information.

The secondary endpoints were:

- Time to total alkaline phosphatase (ALP) progression defined as:
  - In patients with no total ALP decline from baseline: a ≥ 25% increase measured at least 12 weeks from baseline,
  - In patients with initial total ALP decline from baseline: a ≥ 25% increase above the nadir value, confirmed by a second value obtained at least 3 weeks later,
- Total ALP response: reduction of total ALP by at least 30% compared to baseline value, confirmed by a second total ALP value at least 4 weeks later.
- Time to occurrence of first symptomatic skeletal event: skeletal events were defined as the use of radiation therapy to relieve skeletal symptoms, the occurrence of new symptomatic

[3] Parker C, Nilsson S, Helle SI et col. Alpha emitter radium-223 and survival in metastatic prostate cancer. New Engl J Med 2013; 369(3): 213-23.
[4] The first patient was included on 12 June 2008 and the last on 1 February 2011.

pathological bone fractures (vertebral or non-vertebral), the occurrence of spinal cord compression or the use of tumour-related orthopaedic surgery.
- Total ALP normalisation: return of total ALP value to within normal range 12 weeks after start of treatment (two consecutive measurements at least 2 weeks apart) in patients who had total ALP above the upper limit of normal at baseline.
- Time to PSA progression:
    - In patients with no PSA decline from baseline: a ≥ 25% increase and an increase in absolute value ≥ 2 ng/ml, measured at least 12 weeks from baseline,
    - In patients with initial PSA decline from baseline: a ≥ 25% increase and an increase in absolute value ≥ 2 ng/ml above the nadir value, confirmed by a second value at least 3 weeks later.

- Quality of life: EQ-5D and FACT-P (*Functional Assessment of Cancer Therapy – Prostate*) questionnaires, self-reported questionnaires completed by the patient including items on the physical, familial, social, emotional and functional well-being of the patients (FACT-G score) and items specific to prostate cancer (weight loss, appetite, pain, physical comfort, urinary and intestinal function). Score ranged from 0 to 156

- safety.

The main inclusion criteria were:
- Men aged 18 years or over,
- Histologically or cytologically confirmed adenocarcinoma of the prostate,
- Resistance to castration, defined as:
    - testosterone assay ≥ 50 ng/dl,
    - bilateral prostatectomy or chemical castration,
    - progression of PSA defined by two successive increases of PSA compared with a previous value, each measurement being separated by at least one week,
- PSA ≥ 5 ng/ml,
- At least two bone metastases on the bone scan within the previous 12 weeks,
- No planned chemotherapy within the next 6 months,
- Regular treatment with analgesics for bone pain or external beam radiation therapy for bone pain over the previous 12 weeks,
- ECOG performance status score ≤ 2,[5]
- Life expectancy ≥ 6 months,
- Laboratory values within the limits indicated below:
    - Neutrophils ≥ 1.5 10^9/l,
    - Platelets ≥ 100,000/µl,
    - Haemoglobin ≥ 10.0 g/dl,
    - Bilirubin ≤ 1.5 x ULN (upper limit of normal),
    - ALT and AST ≤ 2.5 x ULN,
    - Creatinine ≤ 1.5 x ULN;
    - Albumin > 25 g/l.

Non-inclusion criteria

The main non-inclusion criteria were:
- Eligible for treatment with docetaxel (patients eligible for treatment, willing to receive it and where docetaxel is available),

[5] The Eastern Cooperative Oncology Group (ECOG) performance status score is used to assess the progression of the disease and its consequences on the patient's quality of life. The score of this test goes from 0 to 5: 0= asymptomatic patients; 1= symptomatic patients, ambulatory without limitation; 2= symptomatic patients, bedridden for < 50% of the day; 3= symptomatic patients, bedridden for > 50% of the day; 4= bedridden; 5= dead

- Treatment with chemotherapy within the previous 4 weeks or planned during the treatment period, or persistent adverse events due to the chemotherapy administered more than 4 weeks ago, apart from neuropathy,
- History of radiotherapy of one side of the body,
- Treatment of bone metastases with radioisotopes during the previous 24 weeks,
- Previous treatment with radium-223,
- Transfusion or administration of erythropoietin during the previous 4 weeks,
- History of cancer during the previous 5 years,
- History of visceral metastasis, or visceral metastases confirmed by CT or chest x-ray within the previous 8 weeks,
- Malignant lymphadenopathies > 3 cm,
- Risk of spinal cord compression or spinal cord compression observed on the physical examination or magnetic resonance imaging (MRI),
- Severe condition such as uncontrolled infection, heart failure (NYHA III or IV), Crohn's disease or ulcerative colitis, myelodysplasia.

A subgroup analysis of the primary efficacy endpoint was planned in the ITT population only, to conform the choice of criteria, depending on the stratification criteria (ALP < 220 IU/l versus ≥ 220 IU/l), concomitant treatment with bisphosphonate (yes/no) and previous treatment with docetaxel (yes/no) and the following covariates at inclusion:
- ECOG performance status score (0 and 1 versus 2),
- Spread of the disease (number of foci with increased uptake),
- Absence / presence of pain,
- Treatment (yes/no) with opioids.
- Ethnicity

Results:

The 809 randomised patients (541 patients in the XOFIGO group and 268 patients in the placebo group) had a median age of 71 years. The majority (87%) of the patients had an ECOG performance status score of 0 or 1. Almost half of the patients (46%) did not present any pain (2%) or level 1 pain (43.4%) according to the WHO classification (asymptomatic or mildly symptomatic) and 54% presented level 2-3 pain according to the WHO classification.
A slight imbalance was observed between the placebo group and the XOFIGO group on:

- the extent of the metastases: 48.1% of patients with 6 to 20 foci with increased uptake versus 43.5%;
- median PSA: 195.15 versus 159.05 µg/l.

Table 1: Main characteristics of patients in the study (ITT population)

		XOFIGO N = 541	Placebo N = 268
Age (years), n		541	268
Mean (SD)		70.2 (8.08)	70.7 (7.81)
Median		71.0	70.5
Min – Max		49-90	44-94
Distribution [n (%)]	< 65 years	139 (25.7)	65 (24.3)
	65 – 75 years	252 (46.6)	125 (46.6)
	> 75 years	150 (27.7)	78 (29.1)
Ethnicity [n (%)]	White (Caucasian)	507 (93.7)	252 (94.0)
	White (Hispanic)	0	1 (0.4)
	Black (African American)	10 (1.8)	3 (1.1)
	Asian	19 (3.5)	12 (4.5)
	Other	5 (0.9)	0
Weight (kg)	n	537	266
	Mean (SD)	82.9 (14.8)	82.5 (14.9)
	Median	82.0	81.9
	Min – Max	40-139	47-130
Total ALP [n (%)]	<220 U/l	305 (56.4)	147 (54.9)
	≥ 220 U/l	236 (43.6)	121 (45.1)
Treatment with bisphosphonates [n (%)]	Yes	220 (40.7)	111 (41.4)
	No	321 (59.3)	157 (58.6)
Previous treatment with docetaxel [n (%)]	Yes	314 (58.0)	156 (58.2)
	No	227 (42.0)	112 (41.8)
ECOG PS [n (%)]	0	137 (25.4)	62 (23.2)
	1	330 (61.2)	167 (62.5)
	2	71 (13.2)	37 (13.9)
	3	1 (0.2)	1 (0.4)
	Missing, n	2	1
WHO analgesic scale [n (%)]	0	12 (2.2)	2 (0.7)
	1	235 (43.4)	124 (46.3)
	2	132 (24.4)	72 (26.9)
	3	162 (29.9)	70 (26.1)
External beam radiation therapy* [n (%)]	Yes	91 (16.8)	42 (15.7)
	No	450 (83.2)	226 (84.3)
Treatment with opioids [n (%)]		54 (10.0)	21 (7.8)
PSA (µg/l)	n	490	250
	Mean (SD)	437.14 (832.77)	524.43 (1215.05)
	Median	159.05	195.15
	Min – Max	3.8-6026.0	1.5-14,500.0
Albumin (g/l)	n	539	268
	Mean (SD)	39.4 (4.62)	39.5 (4.72)
	Median	40.0	40.0
	Min – Max	24-53	23-50
Haemoglobin (g/dl)	n	541	268
	Mean (SD)	12.09 (1.460)	12.06 (1.493)
	Median	12.20	12.10
	Min – Max	8.5-15.7	8.5-16.4
LDH (U/l)	n	535	267
	Mean (SD)	394.0 (277.20)	445.2 (420.80)
	Median	317.0	328.0
	Min – Max	76-2171	132-3856
Total ALP (U/l)	n	541	268
	Mean (SD)	369.3 (460.32)	382.2 (477.48)
	Median	213.0	224.0
	Min – Max	32-4661	29-3225

*: during the 12 weeks prior to pre-inclusion, LDH: lactate dehydrogenase.

Table 2: Characteristics of the prostate cancer and the previous treatments (ITT population)

	Interim analysis			Updated analysis before crossover		
	XOFIGO n = 541	Placebo n = 268	Total n = 809	XOFIGO n = 614	Placebo n = 307	Total n = 921
Time since prostate cancer diagnosis (months), n	481	235	716	543	271	814
Mean	69.54	61.78	66.99	69.36	63.84	67.52
SD	(46.65)	(47.38)	(47.00)	(46.431)	(48.793)	(47.272)
Median	59.03	51.13	56.67	58.83	52.00	56.82
Range	7.6-312.5	1.2-347.2	1.2-347.2	7.6-312.5	1.2-347.2	1.2-347.2
Time since metastasis diagnosis (months), n	467	224	691	526	258	784
Mean	30.25	30.23	30.24	30.51	30.05	30.36
SD	(26.96)	(27.22)	(27.03)	(27.234)	(27.052)	(27.158)
Median	24.57	23.27	24.17	24.80	22.03	23.93
Range	0.0-254.2	0.2-183.2	0.0-254.2	0.0-254.2	0.2-183.2	0.0-254.2
Combined Gleason score at time of diagnosis, n	472	235	707	542	270	812
Mean	7.5	7.8	7.6	7.5	7.7	7.6
SD	1.29	1.21	1.27	1.25	1.30	1.27
Median	7.0	8.0	8.0	7.0	8.0	8.0
Range	3-10.	2-10.	2-10.	3-10.	2-10.	2-10.
Extent of the metastases, n (%)						
1 (< 6 foci of increased uptake)	88 (16.3)	33 (12.3)	121 (15.0)	100 (16.4)	38 (12.4)	138 (15.0)
2 (6-20 foci of increased uptake)	235 (43.5)	129 (48.1)	364 (45.0)	262 (42.9)	147 (48.0)	409 (44.6)
3 (> 20 foci of increased uptake)	169 (31.3)	80 (29.9)	249 (30.8)	195 (31.9)	91 (29.7)	286 (31.2)
4 (superscan appearance)	48 (8.9)	26 (9.7)	74 (9.2)	54 (8.8)	30 (9.8)	84 (9.2)
Missing	1	0	1	3	1	4
≥ 2 foci of increased uptake	541 (100.0)	267 (99.6)	808 (99.9)	610 (100.0)	305 (99.7)	915 (99.9)
Previous treatments, n (%)	534 (98.7)	264 (98.5)	798 (98.6)	605 (98.5)	303 (98.7)	908 (98.6)
Radical prostatectomy	103 (19.0)	26 (9.7)	129 (15.9)	119 (19.4)	31 (10.1)	150 (16.3)
Prostate - external beam radiation therapy	191 (35.3)	75 (28.0)	266 (32.9)	215 (35.0)	89 (29.0)	304 (33.0)
Brachytherapy	14 (2.6)	8 (3.0)	22 (2.7)	15 (2.4)	9 (2.9)	24 (2.6)
Bilateral orchiectomy	82 (15.2)	44 (16.4)	126 (15.6)	94 (15.3)	49 (16.0)	143 (15.5)
LHRH analogues	184 (34.0)	81 (30.2)	265 (32.8)	213 (34.7)	97 (31.6)	310 (33.7)
Antiandrogens	469 (86.7)	229 (85.4)	698 (86.3)	532 (86.6)	264 (86.0)	796 (86.4)
Chemotherapy	319 (59.0)	157 (58.6)	476 (58.8)	357 (58.1)	175 (57.0)	532 (57.8)
Bisphosphonates	98 (18.1)	47 (17.5)	145 (17.9)	121 (19.7)	56 (18.2)	177 (19.2)
Systemic radiotherapy	21 (3.9)	8 (3.0)	29 (3.6)	24 (3.9)	8 (2.6)	32 (3.5)
Bone - external beam radiation therapy	274 (50.6)	129 (48.1)	403 (49.8)	306 (49.8)	149 (48.5)	455 (49.4)
Other	140 (25.9)	70 (26.1)	210 (26.0)	162 (26.4)	84 (27.4)	246 (26.7)

LHRH: Luteinizing-hormone-releasing hormone.

Result for the primary endpoint:

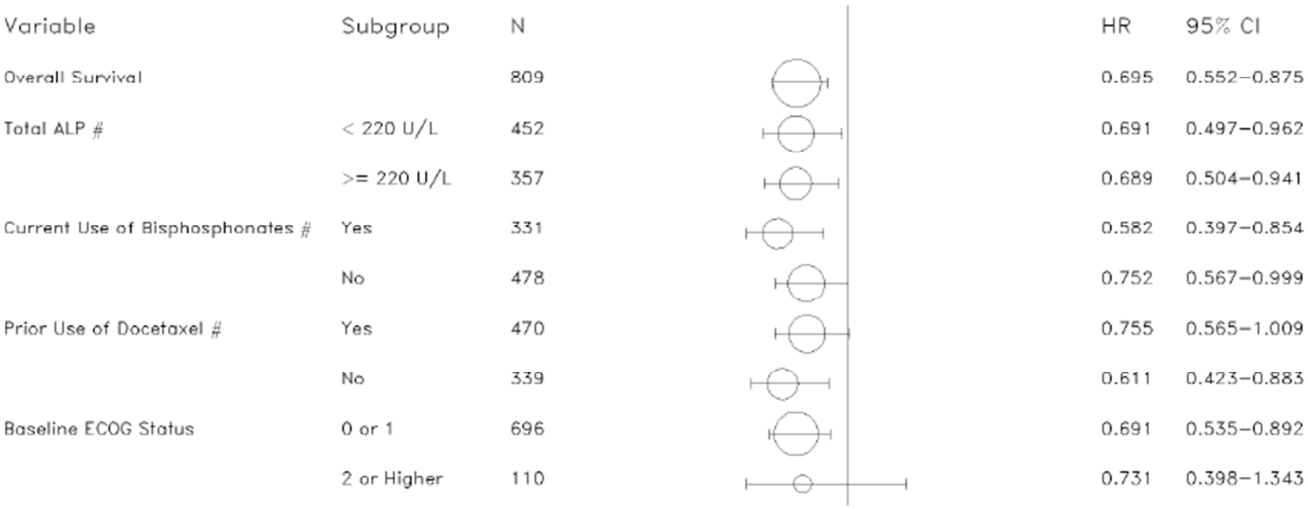
Table 3: Overall survival results (primary endpoint)

	XOFIGO	**Placebo**
Interim analysis	n = 541	n = 268
Number (%) of deaths	191 (35.3%)	123 (45.9%)
Median overall survival in months 95% CI	14.0 [12.1-15.8]	11.2 [9.0-13.2]
Hazard ratio[b] CI 95 %	0.695 [0.552-0.875]	
p-value[a] (2-sided)	0.00185	

On the date of the interim analysis planned in the protocol corresponding to the main study analysis, 191 (35.3%) of the XOFIGO group patients and 123 (45.9%) of the placebo group had died.

The median overall survival was longer in the XOFIGO group (14 months than in the placebo group (11.2 months) which is an absolute difference of 2.8 months and a hazard ratio of 0.695 95% CI: [0.552; 0.875].
A higher percentage of deaths not linked to prostate cancer was observed in the placebo group (8.6% in the placebo group versus 4.8% in the XOFIGO group).

Results of the overall survival in the different planned subgroups.



An updated descriptive analysis before crossover with an additional 9-month follow-up and 921 patients suggested a median overall survival of 14.9 months in the XOFIGO group and 11.3 months in the placebo group (HR 0.695 95% CI: [0.581-0.832]).

Secondary endpoint results

Table 4: Secondary efficacy endpoints (interim analysis)

			Incidence rate [no. (%) of patients]		**Analysis of the time to event occurrence** [median in months]			
			XOFIGO n = 541	**Placebo** n = 268	**XOFIGO** n = 541	**Placebo** n = 268	**Hazard Ratio** (95% CI) < 1 in favour of XOFIGO	**p**
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 criteria	**External beam radiation therapy 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
		Surgery	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 evaluable; PSA = prostate-specific antigen; SSE = symptomatic skeletal event.

a Defined by the occurrence of one of the following events: external beam radiation therapy for pain relief, pathological bone fracture, spinal cord compression, or tumour-related orthopaedic surgery.
b Not evaluable due to an insufficient number of events beyond the median.
c Defined as a ≥ 25% increase compared with the baseline/nadir.
d Defined as a ≥ 25% increase and an increase of the absolute value ≥ 2 ng/ml compared with the baseline/nadir.

- time to total alkaline phosphatase progression

The median time to total ALP progression was not yet reached in the XOFIGO group and was 3.7 months 95% CI: [3.5; 4.1] in the placebo group (hazard ratio 0.162, 95% CI: [0.120; 0.220], p < 0.00001).

- response of total alkaline phosphatase (ALP)

Confirmed reduction by at least 30% of the total ALP after 12 weeks was noted in 43.3% of patients in the XOFIGO group versus 2.5% of those in the placebo group p < 0.001.

- time to occurrence of first symptomatic skeletal event

The median time to occurrence of first skeletal event was longer in patients treated with XOFIGO, 13.5 months versus 8.4 months which is an absolute difference of 5.1 months (hazard ratio 0.610, 95% CI: [0.461; 0.807], p = <0.00046).
The use of external beam radiation therapy for analgesia was noted in 22.6% of patients in the XOFIGO group versus 26.9% of patients in the placebo group.
The median time to use of analgesic radiotherapy was 17 months in the XOFIGO group versus 10.8 months in the placebo group (hazard ratio 0.670, 95% CI: [0.525; 0.854], p = 0.001).
The median time was not reached in either of the two groups for the spinal cord compression, surgery and bone fracture criteria.

- total alkaline phosphatase normalisation

The percentage of patients with total ALP normalisation after 12 weeks was 32.9% in the XOFIGO group versus 0.9% in the placebo group, p < 0.001.

- Time to PSA progression

The median time to PSA progression was 3.6 months in the XOFIGO group versus 3.4 months in the placebo group which is a difference of 0.2 months.

- quality of life

Quality of life was assessed using specific questionnaires: the EQ-5D questionnaire (generic questionnaire) and the FACT-P questionnaire (prostate-cancer-specific questionnaire). A decline in quality of life was observed in both groups. Compared with the placebo, this decline, as measured by the EQ-5D utility score (0.040 versus -0.109; p = 0.001), and the EQ-5D visual analogue scale score (2.661 versus -5.860; p = 0.018) and the FACT-P total score (3.880 versus -7.651; p = 0.006), was slower in the group treated with XOFIGO during the period on treatment. Nevertheless, the observed difference did not reach the threshold considered to be clinically relevant.
Pain evaluation was not performed in this study.

08.2 Adverse effects

The safety analysis presented below focuses on safety data from the updated analysis before crossover (600 in the XOFIGO group, 301 in the placebo group).
Adverse event-related treatment discontinuations were 16.5% in the XOFIGO group versus 20.6% in the placebo group.
The adverse events observed more commonly in the XOFIGO group than in the placebo group were diarrhoea (25.2 versus 15.0%), thrombocytopaenia (11.5 versus 5.6%) and neutropaenia (5.0 versus 1.0%),
The most common grade 3/4 adverse events were bone pain (XOFIGO: 20.8%, placebo: 25.6%) and anaemia (XOFIGO: 12.8%, placebo: 13.0%).

The most common serious adverse events were: tumour progression (XOFIGO 11.0%, placebo: 12.0%), bone pain (10.0% and 16.3% respectively), anaemia (8.2% and 8.6% respectively) and spinal cord compression (3.5% and 5.3% respectively).

08.3 Summary & discussion

A double-blind, phase III study compared the efficacy and safety of radium dichloride (XOFIGO) versus a placebo, both associated with an optimal standard of care chosen by the investigator (including external beam radiation therapy, bisphosphonates, corticosteroids, oestrogens, antiandrogens, estramustine or ketoconazole) in patients with castration-resistant prostate cancer with symptomatic bone metastases. The presence of visceral metastases or malignant lymphadenopathy exceeding 3 cm is a non-inclusion criterion for the study.

The patients were randomised according to a 2:1 design to be treated with an IV bolus of radium-223 dichloride at a dose of 50 kBq/kg or a placebo, in combination, if necessary, with best standard of care.
The patients received six administrations of the study treatment (radium-223 dichloride or placebo) with an injection every 4 weeks, at a dose of 50 kBq/kg.
The 809 randomised patients (541 patients in the XOFIGO group and 268 patients in the placebo group) had a median age of 71 years.
Almost half of the patients (46%) did not present any pain or level 1 pain according to the WHO classification (asymptomatic or mildly symptomatic) and 54% presented level 2-3 pain according to the WHO classification.
A slight imbalance was noted between the two groups for:
- the extent of the metastases, greater in the placebo group than in the XOFIGO group (6-20 foci of increased uptake: 48.1 versus 43.5%
- the median PSA: 195.15 vs 159.05 µg/l in the XOFIGO group

During the interim analysis, the median overall survival (primary endpoint) was longer in the XOFIGO group (14 months) than in the placebo group (11.2 months) which is an absolute difference of 2.8 months and a hazard ratio of 0.695 95% CI: [0.552; 0.875].
A higher percentage of deaths not linked to prostate cancer was observed in the placebo group (8.6% in the placebo group versus 4.8% in the XOFIGO group).

Median time to occurrence of first skeletal event was longer in patients treated with XOFIGO; 13.5 months versus 8.4 months which is an absolute difference of 5.1 months (hazard ratio 0.610, 95% CI: [0.461; 0.807], p = 0.00046).
The median time to PSA progression was 3.6 months in the XOFIGO group versus 3.4 months in the placebo group which is a difference of 0.2 months.
The median time to total alkaline phosphatase progression was not yet reached in the XOFIGO group and was 3.7 months in the placebo group (hazard ratio 0.162, 95%CI: 0.120; 0.220, p <0.00001).
Quality of life, evaluated using the EQ-5D questionnaire (generic questionnaire) and the FACT-P questionnaire (prostate cancer specific questionnaire), revealed decline in both groups.

The adverse events observed more commonly in the XOFIGO group than in the placebo group were diarrhoea (25.2 versus 15.0%), thrombocytopaenia (11.5 versus 5.6%) and neutropaenia (5.0 versus 1.0%),
The most common grade 3/4 adverse events were bone pain (XOFIGO: 20.8%, placebo: 25.6%) and anaemia (XOFIGO: 12.8%, placebo: 13.0%).

It should be noted that the choice of a placebo as a comparator in this study appears questionable since at the time of the study, there were two radioisotopes available (strontium (89Sr) chloride and samarium (153Sm) linked to a bisphosphonate) indicated in the treatment of bone metastases from prostate cancer, albeit limited to the analgesic effect because the impact on overall survival of these two medicinal products has not been studied. In addition, the therapeutic strategy has advanced in

recent years with the integration of abiraterone acetate (ZYTIGA) since 18 December 2012 in the treatment of patients with metastatic prostate cancer who are mildly symptomatic (most intense pain score experienced during the previous 24 hours < 3 on the VAS scale from 0 to 10), after failure of androgen deprivation therapy and in whom chemotherapy is not yet clinically indicated.

08.4 Planned studies

A risk management plan (RMP) has been prepared as part of the European registration of XOFIGO to ensure monitoring of identified or potential risks linked to the use of the product under actual conditions of use. It will also provide missing information on the safety of the proprietary medicinal product.

This RMP will focus on monitoring the following points:

- a significant identified risk: bone marrow toxicity with a risk of insufficient production of blood cells,
- significant potential risks: late-onset bone marrow toxicity, myelodysplastic syndrome/acute myeloid leukaemia (AML), bone sarcoma, secondary neoplastic tumours (apart from myelodysplasia, AML and bone sarcoma), osteonecrosis of the jaw, use without MA in women and children and use of a different dosage to that stated in the MA with additional cycles and higher doses,
- the following missing information: reproductive toxicity in men in metastatic castration-resistant prostate cancer but also in women in the case of use without MA, toxicity on the development of children during use without MA and data on clinical safety in patients with inflammatory gastrointestinal disease and in ethnic groups without white skin.

It should be noted that in addition to routine pharmacovigilance monitoring and presentation of the conclusions from continuous monitoring in the periodic safety update reports (PSURs), the results of ongoing clinical studies (Table 24) and long-term monitoring in actual conditions of use (study 16913) will enable additional characterisation of the incidence and severity of the following potential risks: late-onset bone marrow toxicity, myelodysplastic syndrome, acute myeloid leukaemia (AML), bone sarcoma, secondary neoplastic tumours.
In addition, a study on the use of XOFIGO to monitor the use without MA will be performed using data from Swedish registries.

No measures to minimise specific risks have been planned apart from those listed in the XOFIGO summary of product characteristics.

Table 5: Additional pharmacovigilance activities to answer specific questions about safety described in the RMP and measure the efficacy of risk minimisation measures

Description of monitoring measures	Schedule
BC1-06 (ALSYMPCA study): Longer-term results	Study report: 2015
Studies 15995 and 16216: Early access programme (in the USA, Europe, Israel, Canada, Mexico and Russia respectively)	End-of-study reports 2015
16913: observational safety study (*post authorisation safety study*)	Start: T1 2014 1st interim report end of 2017 Study report: end of 2024
Study on the use of XOFIGO according to data from Swedish registries	Start: June 2014 Study report: end of 2017

09 THERAPEUTIC USE

Castration-resistant prostate cancer (CRPC) corresponds to the advanced stage of the metastatic disease. It is defined as biological and clinical progressive relapse despite effective castration. Castration-resistance generally occurs within 18 to 24 months after the initiation of androgen deprivation therapy in metastatic patients.[6]
CRPC is a very heterogeneous disease with patients presenting very different median survival. However, at the metastatic stage, the median survival does not exceed 18 months and is 9 to 12 months in cases of extensive metastases.
The first stages of castration-resistant prostate cancer (CRPC) with bone metastases are associated with significant pain (35% of patients) and an elevated level of prostate-specific antigen (PSA) in 90% of patients.

In patients with visceral involvement, chemotherapy with docetaxel is offered as a first-line treatment. For patients not able to receive docetaxel, mainly due to their age or general state of health not enabling them to tolerate the cytotoxic adverse effects (in particular neutropaenia), the mitoxantrone and corticosteroid combination can be offered.

In asymptomatic patients, there is no evidence to justify the early initiation of chemotherapy, which must be discussed individually and balanced against simple monitoring (treatment abstention).

In mildly symptomatic patients (most intense pain score experienced during the last 24 hours < 3 on the VAS scale from 0 to 10), abiraterone acetate (ZYTIGA) is a first-line treatment after failure of androgen deprivation therapy and for whom chemotherapy is not yet clinically indicated.

Two radioisotopes (strontium (89Sr) chloride and samarium (153Sm) linked to a bisphosphonate) are also indicated in the treatment of bone metastases from prostate cancer. They target bone metastases and their indication is limited to the analgesic effect because the impact of these two medicinal products on overall survival has not been studied.

XOFIGO represents a new therapeutic option in patients with castration-resistant prostate cancer, symptomatic bone metastases and no visceral or lymphatic involvement (malignant lymphadenopathy exceeding 3 cm). In the absence of data, its role in the chronological sequence compared with abiraterone acetate in patients presenting only bone metastases is unclear.
It should be noted that no data is available on XOFIGO combined with other specific treatments (cytotoxic or hormonal). Similarly, patients included in the ALSYMPCA study must not have received chemotherapy within the 4 weeks prior to inclusion or receive chemotherapy in the 6 months following inclusion.

[6] Salomon L, Azria D, Bastide C et col. Recommandations en onco-urologie 2010 : cancer de la prostate. Progrès en Urologie 2010 ; 20(suppl.4) : S217-S252.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Bone complications in patients with prostate cancer with bone metastases can severely affect the patients' quality of life. They can be life-threatening, particularly through spinal cord compressions.
◗ This proprietary medicinal product is intended as specific curative therapy for bone metastases in prostate cancer.
◗ The efficacy/adverse effects ratio is high.

◗ Public health benefit:
In France, the incidence of prostate cancer is estimated at 56,841 new cases per year.
In France, the public health burden of prostate cancer is therefore major (about 380,000 DALYs Eurozone A, 2004). Despite the smaller number of patients progressing towards or diagnosed at the metastatic stage, this burden in the sub population of patients with castration-resistant prostate cancer with symptomatic metastases and likely to receive XOFIGO is moderate because of the associated significant mortality.
Improving the management quality of cancer patients and their quality of life is a public health need which is an established priority (objective 49 of the Law of 9 August 2004 on public health policy, Cancer Plan 2014-2019, Plan to improve the quality of life of patients with chronic diseases 2007-2011).
In light of the available results from the phase III study of XOFIGO versus placebo, in combination with best standard of care in both groups, which in particular reveal an absolute gain of 2.8 months in overall survival and a gain in terms of time to occurrence of the first symptomatic skeletal event, it is expected that XOFIGO will have an impact in terms of reducing morbidity and mortality compared with the placebo. The expected impact on quality of life preservation remains difficult to assess; improvement of observed time to the decline of the FACT-P score and the EQ-5D utility score was not considered clinically relevant and in the absence of pain assessment.
In the absence comparative data versus currently used treatments indicated in bone metastases, namely the two existing isotopes (for analgesia only) and ZYTIGA (mainly anti-tumour), the expected impact of XOFIGO in terms of reducing morbidity and mortality, and quality of life compared with these currently used treatments cannot be quantified. It is not certain that the results versus placebo presented in the pivotal, study could be transposed to clinical practice.
Finally, no impact on the organisation of care is expected.
Consequently, the proprietary medicinal product XOFIGO is not able to meet an identified public health need and the expected impact of XOFIGO on public health cannot be quantified.

◗ It is a first-line therapy.
◗ Alternative medicinal products exist.

Taking account of these points, the Committee considers that the actual benefit of XOFIGO is substantial in the treatment of castration-resistant prostate cancer, with symptomatic bone metastases and no known visceral metastases.

010.2 Improvement in Actual Benefit (IAB)

XOFIGO provides a minor improvement in actual benefit (IAB IV) compared with a placebo in the treatment of castration-resistant prostate cancer, with symptomatic bone metastases and no known visceral metastases.

010.3 Target population

The target population of XOFIGO is represented by patients with castration-resistant prostate cancer, symptomatic bone metastases and no visceral involvement.

Estimation of the XOFIGO target population can be performed according to the following steps.
The population of patients with metastatic prostate cancer corresponds to two subgroups:

- patients diagnosed at the metastatic stage from the outset;
- patients initially diagnosed at the localised or locally advanced stage and having subsequently progressed to a metastatic stage.

Patients diagnosed at the metastatic stage:
In France, the incidence of prostate cancer was estimated at 71,577 new cases per year in 2010.
According to a study provided for the French parliamentary office for the assessment of health policies (OPEPS) on prostate cancer, the estimated proportion of each stage at diagnosis is:

- 84% for localised stages;
- 3% for locally advanced stages;
- 10% for metastatic stages.

The number of patients with prostate cancer diagnosed as metastatic from the outset can therefore be estimated at 7160 patients.

Patients at the localised stage at diagnosis progressing towards a metastatic stage:
In these patients, the percentage of progression towards a metastatic stage at 5 years is 5% at the prostate-localised stage (clinical stage T1 in the TNM clinical staging system), and it is between 22 and 32% at the capsular invasion stage (clinical stage T2).[7] Based on the distribution of clinical stages at diagnosis, T1 (27%) and T2 (58%), reported in the OPEPS study, the percentage of progression from the localised stage to the metastatic stage would be around 20%.
The number of prostate cancer patients diagnosed at the localised stage and progressing towards a metastatic stage can be estimated at 12,030 patients.

Patients at the locally advanced stage at diagnosis progressing towards a metastatic stage:
Locally advanced tumours have a rate of progression towards a metastatic stage of roughly 40% at 5 years.[8] The number of prostate cancer patients diagnosed at the locally advanced stage and progressing towards the metastatic stage is estimated at 860.
In all, the number of patients at the metastatic stage is estimated at 20,050 per year (7160 + 12,030 + 860).

Metastatic, castration-resistant patients:
96% of patients with metastatic prostate cancer are treated with hormone therapy, i.e. 19,250 patients treated for their metastatic prostate cancer. Of these, 48% become castration-resistant, i.e. 9240 metastatic, castration-resistant patients. Of the castration-resistant patients, 60% are symptomatic and are likely to receive chemotherapy.[9]

[7] Avancès C. Cancer de la prostate: la maladie localisée. Médecine Nucléaire. 2008; 32: 46-50.
[8] Soulié M et al. Place de la chirurgie dans les tumeurs de la prostate à haut risque. Cancer/Radiothérapie 2010;14: 493-9.
[9] TC opinion on JEVTANA 2012.

Around 40% will supposedly present symptomatic bone metastases only and receive treatment with XOFIGO, i.e. around 3700 patients per year.

The target population for XOFIGO is estimated at around 3700 patients per year.

011 COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication "treatment of adults with castration-resistant prostate cancer, with symptomatic bone metastases and no known visceral metastases" and at the dosage in the Marketing Authorisation.

◗ Packaging

It is appropriate for the prescribing conditions according to the indication and the dosage in the MA.