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TRANSPARENCY COMMITTEE

Opinion

1 October 2014

METASTRON, solution for injection, strontium (^{89}Sr) chloride

1 glass vial of 4 ml (CIP: 34009 558 012 0 7)

Applicant: GE HEALTHCARE SAS

INN	Strontium (^{89}Sr) chloride
ATC code (2013)	V10BX01 (Various pain palliation radiopharmaceuticals)
Reason for the review	**Re-assessment of the IAB following joint referral by the Directorate-General for Health, the Social Security Directorate and the Directorate-General for Health Services on 10 October 2013, and in accordance with Article R 163-19 of the French Social Security Code.**
List(s) concerned	**Hospital use (French Public Health Code L.5123-2)**
Indication(s) concerned	**"METASTRON is used as an adjunct or alternative to external radiotherapy in the palliative treatment of pain associated with bone metastases secondary to prostate cancer in patients in whom hormone therapy has failed.** **Before the injection of METASTRON it is necessary to confirm the presence of bone metastases which take up technetium-99m-labelled diphosphonate."**

Actual Benefit	**Low**
Improvement in Actual Benefit	**The proprietary medicinal product METASTRON, as an adjunct or alternative to radiotherapy, does not provide any improvement in actual benefit (IAB V, nonexistent) in the strategy for the management of pain from bone metastases associated with prostate cancer in patients in whom hormone therapy has failed.**
Therapeutic use	**When purely analgesic radioisotope treatment is considered for patients who have pain associated with bone metastases of prostate cancer that take up contrast on bone scan, METASTRON retains a benefit in hyperalgesic patients in whom hormone therapy has failed and whose pain is not controlled by the usual analgesics (opioids). However, its role might be limited by the availability of new therapeutic alternatives such as a radioisotope (XOFIGO) which has shown that it has a favourable effect on survival.**
Target population	**The population likely to benefit particularly from METASTRON is, according to the experts, of the order of 370 patients.** **Very marginal use of this proprietary medicinal product has been observed; 45 vials were sold in 2012 and breaks in supply were reported in 2013.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	24 March 1993 (equivalent mutual recognition procedure)
Prescribing and dispensing conditions /special status	Medicinal product reserved for hospital use. Radiopharmaceuticals may be used only by qualified persons. They may be supplied only to doctors who have obtained the special authorisation provided for in Article R 1333-24 of the French Public Health Code.

ATC Classification	2013	
	V	Various
	V10	Therapeutic radiopharmaceuticals
	V10B	Pain palliation (bone seeking agents)
	V10BX	Various pain palliation radiopharmaceuticals
	V10BX01	Strontium (^{89}Sr) chloride

02 BACKGROUND

As part of the work of updating the list of chargeable medicinal products in addition to hospital services by the Hospitalisation Council, and pursuant to Article R 163-19 of the French Social Security Code, the Directorate-General for Health, the Social Security Directorate and the Directorate-General for Health Services have applied to HAS for a ruling on the IAB of proprietary medicinal products, including the proprietary medicinal product METASTRON, the subject of this Opinion.

METASTRON is a radiopharmaceutical (a medicinal product containing a radioactive substance) the active ingredient of which is strontium (89Sr) chloride. The distribution of strontium in the body is similar to that of the calcium ion, particularly as regards its uptake in bone.

METASTRON was the first β-emitter radiopharmaceutical for palliative use in bone pain to obtain Marketing Authorisation. Its Marketing Authorisation in France is dated 24 March 1993, its approval for hospital use is dated 8 July 1993 and it went on the market on 19 August 1993. The Transparency Committee's Opinion of 1993 did not specify any AB or IAB.

Its use in France is marginal: 45 vials were sold in 2012 and supply problems were reported in 2013.

03 THERAPEUTIC INDICATION

"METASTRON is used as an adjunct or alternative to external radiotherapy in the palliative treatment of pain associated with bone metastases secondary to prostate cancer in patients in whom hormone therapy has failed.
Before the injection of METASTRON it is necessary to confirm the presence of bone metastases that take up technetium-99m-labelled diphosphonate."

04 DOSAGE

“METASTRON is supplied as an aqueous solution for intravenous injection and must be used undiluted. The recommended dose is 150 MBq per injection.
In patients who are particularly fat or very thin, it is also possible to use a dose of 2 MBq/kg “fat-free” body mass. This dose is appropriate for the elderly.
A minimum period of three months must be left between two successive injections of METASTRON.
Re-administrations are not indicated in patients who have not responded to previous treatment with METASTRON. METASTRON should not be administered to children.”

05 CONTRAINDICATIONS AND WARNINGS

5.1. Contraindications

“Use of this product is not recommended in patients with a bone marrow disorder, characterised in particular by neutropenia and/or thrombocytopenia. Under these circumstances, the risk/benefit ratio must be favourable and the resulting benefit of treatment must be considered greater than the risks involved.

METASTRON must not be used as first-line treatment of spinal-cord compression secondary to spinal metastases for which external radiotherapy or surgery may be indicated.”

5.2. Special warnings and precautions for use

“Radiopharmaceutical medicinal products may be handled only by qualified personnel who have been authorised by the competent authorities to use radionuclides.

Radiopharmaceuticals may be received, used and administered only by authorised persons in specially equipped and licensed premises. The receipt, storage, use, transfer and disposal of radiopharmaceuticals are subject to the regulations in force and to the appropriate authorisations of the competent national or local authorities.

Because of its primarily urinary route of elimination, METASTRON should not be administered to patients with severe renal impairment or those likely to have episodes of urinary retention.

In patients with urinary incontinence, the insertion of a bladder catheter must be considered before and after the administration of METASTRON to reduce the risks of radioactive contamination. The international guidelines on the disposal of radioactive waste must be followed.

A haematological assessment should be made of patients, particularly their platelets, before starting treatment.

If repeated administration of METASTRON is being considered, the patient’s haematological response to the initial dose and checks for thrombocytopenia or any other kind of complaint should be carefully taken into account.

In a patient previously treated with METASTRON, the administration of a cytotoxic agent may be considered, provided that the haematological status and leucocyte count are within the normal range. An interval of 12 weeks should be left between the administration of the two treatments.

It generally takes a period of 10-20 days after the administration of METASTRON before an analgesic effect is first observed. This should be borne in mind in patient management and the administration of METASTRON is not recommended in patients with a very short life expectancy.

The haematological status should be assessed carefully before using METASTRON in patients who have previously received, for the same reasons, extensive external irradiation and/or another radiopharmaceutical given for the same therapeutic purpose.

It is important to inform the patient, his/her caregivers and the nursing staff of the usual, associated safety precautions. To this end the patient should be given the product information leaflet.

Haematological monitoring should be carried out regularly for at least 8 weeks after the injection.

The advice of the person responsible for radiological protection should be sought before autopsy or incineration when significant quantities of strontium-89 are likely to be present in a dead patient. These operations do not normally constitute a significant radiological risk."

06 THERAPEUTIC NEED

Castration-resistant prostate cancer (CPRC) is the advanced stage of the metastatic disease. It is defined as a laboratory or clinical recurrence despite effective castration. Historically, the concept of castration resistance does not include the use of the new anti-androgens such as enzalutamide and abiraterone acetate. It generally occurs within a period of 18-24 months after the initiation of androgen suppression in metastatic patients.[1]
CPRC is a very varied disorder; patients' median survival rates differ greatly. However, in the metastatic stage the median survival rate does not exceed 18 months, and is 9-12 months in cases with extensive metastases.
About 50% of patients with prostate cancer develop bone metastases within 30 months, and 80% do so within 5 years. The initial stages of castration-resistant prostate cancer (CRPC) with bone metastases are associated with substantial pain (35% of patients) and increased levels of prostate-specific antigen (PSA) in 90% of cases.[2]

Bone metastases cause numerous complications. Depending on their localisation and bone-marrow impact, they may be responsible for substantial morbidity, particularly bone pain, fractures, medullary compression or haematological complications associated with medullary invasion. Once they become symptomatic, bone metastases very markedly impair patients' quality of life. The pain is often intense and necessitates the use of opioid analgesics or external radiotherapy.

In symptomatic patients who are considered resistant to castration (excluding those on enzalutamide and abiraterone acetate), chemotherapy with docetaxel is offered as first-line treatment. For patients unable to receive docetaxel, mainly on account of their age or because their general condition means that they cannot tolerate the cytotoxic adverse effects (especially neutropenia), a combination of mitoxantrone and corticosteroids can be offered.
In asymptomatic patients, there is no evidence to justify the early initiation of chemotherapy which must be discussed with the individual patient and weighed up against simple monitoring (abstention from treatment).
In patients with few symptoms (score for the most intense pain experienced in the last 24 hours < 3 on a 0-10 visual analogue scale (VAS), abiraterone acetate (ZYTIGA) is a first-line treatment after failure of androgen suppression treatment and for cases in which chemotherapy is not yet clinically indicated.

Two radioisotopes (strontium 89Sr chloride and samarium 153Sm-labelled diphosphonate) are also indicated in the treatment of bone metastases (of prostate cancer for strontium, of all cancers for samarium). They target bone localisations and their indication is limited to the analgesic effect, because the impact of these two medicines on overall survival has not been demonstrated. A third radioisotope (XOFIGO) has in turn shown a favourable effect on overall survival by comparison with placebo.

[1] Salomon L, Azria D, Bastide C et al. Recommandations en onco-urologie 2010: cancer de la prostate [Guidelines on onco-urology, 2010: prostate cancer]: Progrès en Urologie 2010; 20: pp 217-252.
[2] EPAR XOFIGO, p8

07 CLINICALLY RELEVANT COMPARATORS

07.1 Medicinal products

Radiopharmaceutical medicinal proprietary products

Two other radioisotope medicines have an indication in bone metastases of prostate cancer:

- limited to analgesic use like METASTRON, QUADRAMET 1.3 GBq/ml, solution for injection (samarium ^{153}Sm-labelled diphosphonate) the effect of which on overall survival has not been demonstrated. The indication for QUADRAMET is broader than that for METASTRON; it is not limited to prostate cancer;
- XOFIGO 1000 kBq/ml, solution for injection, radium dichloride (Ra-223), Marketing Authorisation of 13 November 2013, the effect of which on overall survival has been assessed and demonstrated versus placebo.
  The Committee thought that XOFIGO provided a minor improvement in actual benefit (IAB IV) by comparison with placebo in the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known gastrointestinal metastases (Opinion of 02.04.2014).

Name (INN) *Company*	Same TC* Yes / No	Indication	Marketing Authorisation	Date of Opinion
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 (99mTc)-labelled bisphosphonates on bone scan."	05.02.1998	NA**
XOFIGO 1000 kBq/ml, solution for injection radium dichloride (Ra-223) BOEHRINGER INGELHEIM FRANCE	Yes	"Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known gastrointestinal metastases."	13.11.2013	2.04.2014

*TC: *therapeutic category
**Not applicable: Marketing Authorisation before the Decree of 27 October 1999 governing the rules for access to reimbursement

Other proprietary medicinal product

Abiraterone acetate (ZYTIGA), in combination with prednisone or prednisolone, also has an indication in the same setting, i.e. patients with metastatic prostate cancer limited to the bone and with few symptoms (most intense pain score recorded within the last 24 hours < 3 on a VAS scale of 0-10), after the failure of androgen suppression treatment and for whom chemotherapy is not yet clinically indicated.

07.2 Other health technologies

External radiotherapy
Orthopaedic surgery

◗ Conclusion

QUADRAMET and XOFIGO can be regarded as clinically relevant comparator isotopes for METASTRON as regards the analgesic effect on bone metastases.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

METASTRON is authorised and reimbursed in many countries in Europe and North America. In France and the United States, the presence of bone metastases must be confirmed before treatment. It is reimbursed in the countries in which it is authorised.

09 SUMMARY OF PREVIOUS ASSESSMENTS

The Committee's Opinion is from 1993 and did not give either an AB or IAB for this proprietary medicinal product.

Indication	Palliative treatment of pain associated with bone metastases of prostate cancer as an adjunct or alternative to radiotherapy in patients in whom hormone therapy has failed.
Date of Opinion (reason for the request)	08 July 1993 (Approval for hospital use and for use by various public services)
Actual Benefit (wording)	NA
Improvement in Actual Benefit (wording)	NA
Therapeutic use	In therapeutic use in metastatic prostate cancer, METASTRON should be used, in accordance with the therapeutic indications in the Marketing Authorisation, at a late stage in the development of the disease (failure of OR non-response to hormone therapy) because of long-term uncertainties about toxicity and the fact that it is not possible to give several administrations of this isotope (more than 2).
Target population (wording)	Patients at an advanced stage of their disease in whom hormone therapy has failed.

010 ANALYSIS OF AVAILABLE DATA

010.1 Efficacy

The company has supplied a reminder of the initial clinical studies on the basis of which METASTRON was included in 1993 and an update to the available data from an analysis of the literature, since no new clinical study has been performed.

Reminder of the clinical studies in the initial dossier:
The Committee's conclusions in 1993 were as follows: "efficacy was demonstrated in 2 clinical trials, the first comparing METASTRON (200 MBq) in radiotherapy showed an analgesic effect of the same order as that obtained with radiotherapy. The second trial which combined METASTRON (400 MBq) and external radiotherapy (half-body or local radiotherapy) by comparison with radiotherapy alone showed that the analgesic effect of METASTRON is added to that of radiotherapy. In a small number of patients, this treatment delays the appearance of new painful sites."

Update of the clinical efficacy data
As part of the re-assessment of METASTRON, the company supplied a bibliographic dossier containing open, non-randomised studies, most of poor methodological quality, performed with small populations, some of them on cancers other than prostate cancer, and consequently these studies will not be described. Other studies comparing METASTRON (^{89}Sr) with radioisotopes that do not have Marketing Authorisation in France (^{188}Re-HEDP and ^{186}Re-HEDP) were supplied but no details will be given. The dossier quotes data on the combination of strontium-89 with different chemotherapies; since METASTRON does not have Marketing Authorisation in combination with chemotherapy, these data will not be taken into account. In addition, other studies evaluating the effect of METASTRON on criteria other than pain or survival were added to the dossier but will not be taken into account because they do not allow an evaluation of the efficacy of METASTRON in the wording of the indication specified by the Marketing Authorisation, i.e. the treatment of pain associated with bone

metastases. A study performed between 1988 and 1991 which is quoted in the dossier, compared efficacy in terms of the pain relief of ^{89}Sr and external radiotherapy; it will not be described because it has already been taken into account in the previous assessment by the Committee. Finally, a systematic literature review published in 2005 was presented but will not be described because it includes only articles published in English (publication bias cannot be ruled out), that are of variable methodological quality (phase I study) and merely lists the results of each study without making a proper meta-analysis that can be used to quantify the effect of ^{89}Sr.

Overall, from among the data included in the dossier concerning METASTRON in the indication in its Marketing Authorisation, namely the treatment of bone pain associated with prostate cancer, two clinical studies were selected:

- study by Baczyk et al (2007)[3]

This randomised study compared the analgesic efficacy of strontium-89 (150 MBq) with that of samarium-153 (^{153}Sm-EDTMP 37 MBq/kg) in 60 men with prostate cancer aged 53-84 years and 40 women with breast cancer aged 48-75 years who had bone metastases.
All patients had a history of treatment with local radiotherapy and/or bisphosphonates. Radiotherapy had to have been stopped for at least 2 months and bisphosphonates for at least 2 weeks before the radioisotope treatment. None of the patients had ever been treated with radioisotope. On inclusion, the patients were receiving treatment with analgesics (NSAIDs and/or opioids) with no satisfactory response.

Only the results for prostate cancer (the only Marketing Authorisation indication for METASTRON) are presented. No difference in analgesic efficacy was revealed between strontium-89 and samarium-153 in these patients in the parameters evaluated:
- the median change in pain measured on a visual analogue scale (range 0-10) evaluated 2 months after treatment was similar in the 2 groups -4 [-8; 2] with ^{89}Sr and -4 [-7; 1] with ^{153}Sm,
- the median change in the Karnofsky performance scale (from 0 to 100) was +20 [-20; +30] with ^{89}Sr and +20 [-30; +30] with ^{153}Sm, and
- the mean change in analgesic use was -55% in the ^{89}Sr group and -45% with ^{153}Sm.

No particular safety signal was observed in this study.

It should be noted that the publication does not include either a calculation of the number of subjects needed or a description of the statistical analyses provided for in the protocol, such that in this context it is tricky to interpret the results from the subgroup of patients with prostate cancer.

- study by Oosterhof et al (2003)[4] et al

This randomised study compared ^{89}Sr (150 MBq) with local radiotherapy in 203 patients with hormone resistant prostate cancer who had bone metastases (101 patients treated with ^{89}Sr and 102 with radiotherapy). This study had multiple objectives: safety, subjective response rate to treatment, time to subjective progression and overall survival. The primary efficacy endpoints were survival and time to progression. The demographic and medical characteristics were comparable in the two groups (median age 71 years).
A statistically significant difference in favour of radiotherapy was found for overall survival: 11 months versus 7.2; p=0.0457. No statistical difference between the 2 groups was found in terms of the time to subjective progression: the median time was 3 months with ^{89}Sr and 3.3 months with radiotherapy (p=NS).

010.2 Adverse effects

[3] Baczyk M et al.89Sr versus 153Sm-EDTMP: of comparison treatment efficacy of painful bone metastases in prostate and breast carcinoma. Nucl Med Commun 2007;28 (4):245-50.

[4] Oosterhof GO et al. Strontium (89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. Eur Urol 2003; 44(5):519-26.

World periodic pharmacovigilance reports covering the period from April 1992 to May 2012 were supplied. Since it first went on the market in 1986, 90,000 vials of METASTRON have been administered around the world. The total number of pharmacovigilance cases reported was 1309, which included 715 serious events. Most of these observations are from Japan (848 cases, 91%) because of the inclusion, since November 2007 at the request of the Japanese authorities, of all patients treated with METASTRON in a post-marketing surveillance study.
About 29% of the adverse effects (AEs) reported concerned blood and lymphatic system disorders such as bone marrow depletion, thrombocytopenia, anaemia or leucopenia. General disorders and administration site conditions, mainly exacerbations of pain, accounted for about 13% of AEs, most often. About 11% of AEs concerned the “Investigations” system organ class; the most common effect was a reduction in the platelet count and in the white cell count. Vascular disorders, mainly flushing after rapid administration (in less than 30 seconds) accounted for about 6% of the cases reported. Cases of disseminated intravascular coagulation (DIC) were reported after the administration of METASTRON, but DIC is a recognised complication of certain malignant diseases.
Changes to the SPC that have not yet been validated by the French National Agency for Medicines and Health Products Safety (ANSM) to complete the safety information (adverse effects heading) and to strengthen the warnings about METASTRON have been in the ANSM assessment process since 2013.

Overall, to date no new safety signal likely to change the known safety profile of this radioisotope has been revealed by the analysis of the available pharmacovigilance data.

010.3 Summary and discussion

During its assessment by the Transparency Committee in 1993, the available data showed the efficacy of METASTRON, strontium-89 chloride, as analgesic treatment of metastatic bone pain from prostate cancer in the stage of hormone therapy failure, with an analgesic effect of the same order as that of radiotherapy in one study.

Since this assessment, the proprietary medicinal product METASTRON has been the subject of numerous publications, although most of them were about clinical studies of poor methodological quality, and some were performed in small populations and/or outside the scope of the indication in its Marketing Authorisation, or have already been taken into account by the Committee in its previous assessment.

Thus, only the results of 2 studies are included in this re-assessment.
The first randomised study compared strontium-89 with the other radioisotope available in France, samarium-153 (QUADRAMET) and did not show any difference in terms of analgesic efficacy between these 2 radioisotopes in the subgroup with prostate cancer.
The second randomised study compared strontium-89 with radiotherapy and showed the superiority of radiotherapy by comparison with strontium-89 in terms of median overall survival: 11 months versus 7.2; p=0.0457. No difference was found between the 2 treatments in terms of the time to progression.

Unlike with XOFIGO, the available data do not provide conclusive proof of the beneficial effect of METASTRON on survival.

In terms of safety, no particular safety signal was revealed. The known potential adverse effects of METASTRON are: a possible increase in pain (transient and improved by analgesics), bone marrow toxicity, the occurrence of thrombocytopenia and leucopenia, a reduction in the platelet count, hot flushes.

010.4 Planned studies

None.

011 THERAPEUTIC USE

In radioisotope treatment for purely analgesic purposes in patients who have pain associated with bone metastases of prostate cancer that take up contrast in scintigraphy, METASTRON retains a benefit particularly in situations where pain is difficult to control with opioid analgesics.

Its role in therapeutic use could, however, be limited by developments in treatment, particularly when another radioisotope that has shown a favourable effect on overall survival, radium 223 (XOFIGO), becomes available.

The number of prescriptions for METASTRON is in practical terms very small, given the number of patients potentially eligible according to the indication in its Marketing Authorisation.

012 TRANSPARENCY COMMITTEE CONCLUSIONS

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

012.1 Actual benefit

◗ Bone complications in patients who have prostate cancer with bone metastases may severely affect patients' quality of life. They may be life-threatening, mainly through medullary compression.
◗ This proprietary medicinal product is intended as specific non-curative treatment of the bone metastases of prostate cancer.
◗ Its analgesic efficacy has been established in previous studies. No beneficial effect on overall survival has been formally demonstrated. Its toxicity is essentially haematological, through myelotoxicity.
Consequently, its efficacy/adverse effects ratio is low.

◗ Public health benefit
The public health burden of the subpopulation of patients with prostate cancer and castration-resistant symptomatic metastases who are likely to receive METASTRON is moderate because of the substantial associated mortality.
The improvement of the quality of management and the quality of life of patients with cancer is a public health need which is an established priority.
In view of the available data, METASTRON continues to provide a response to the identified public health need but its impact on public health cannot be quantified.

◗ This is a purely analgesic treatment which is still of value in hyperalgesic patients in whom hormone therapy has failed and whose pain is not controlled by the usual analgesics (opioids). However, its role might be limited by the availability of new therapeutic alternatives such as a radioisotope (XOFIGO) which has shown that it has a favourable effect on survival.

◗ Alternative medicinal products exist.

Taking account of these points, the Committee considers that the actual benefit of METASTRON is <u>low</u> in the Marketing Authorisation indication, namely: "as an adjunct or alternative to external radiotherapy in the palliative treatment of pain associated with bone metastases secondary to prostate cancer in patients in whom hormone therapy has failed".

012.2 Improvement in actual benefit (IAB)

The proprietary medicinal product METASTRON, as an adjunct or alternative to radiotherapy, does not provide any improvement in actual benefit (IAB V, nonexistent) in the strategy for the management of pain from bone metastases associated with prostate cancer in patients in whom hormone therapy has failed.

012.3 Target population

According to the experts, the population likely to benefit from treatment with METASTRON is represented by patients who have prostate cancer with painful bone metastases and in whom hormone therapy and the usual analgesic treatments have failed.

The target population of METASTRON can thus be estimated in the following stages.
The population of patients with prostate cancer in the metastatic stage consists of two subgroups:

- patients diagnosed with metastatic disease at the outset;
- patients initially diagnosed at the localised or locally advanced stage who have subsequently progressed to a metastatic stage.

Patients diagnosed at the metastatic stage:
In France, the incidence of prostate cancer was estimated, in 2010, at 71,577 new cases per year.
According to a study on prostate cancer provided for the French Parliamentary Office for the Evaluation of Health Policies (OPEPS), the share of stages in the diagnosis is estimated to be:

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

The number of patients with prostate cancer diagnosed in the metastatic stage at the outset can therefore be estimated to be 7160 patients.

Patients diagnosed at the localised stage, progressing to a metastatic stage:
In these patients, the percentage progressing to a metastatic stage at five years is 5% in patients with a stage localised to the prostate (clinical stage T1 in the TNM classification), and it is between 22 and 32% in patients with capsular involvement (clinical stage T2).[5] Based on the distribution of clinical stages T1 (27%) and T2 (58%) reported in the OPEPS study, the percentage progressing from the localised stage to the metastatic stage is about 20%.
The number of prostate cancer patients diagnosed at the localised stage and progressing to a metastatic stage can be estimated to be 12,030 patients.

Patients diagnosed at the locally advanced stage, progressing to a metastatic stage:
Locally advanced tumours have a rate of progression to a metastatic stage of roughly 40% at five years.[6] The number of prostate cancer patients diagnosed at the locally advanced stage and progressing to the metastatic stage is estimated to be 860 patients.
In all, the number of patients at the metastatic stage is estimated to be 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 likely to be receiving chemotherapy.[7]

[5] Avancès C. Cancer de la prostate: la maladie localisée [Prostate cancer: the localised disease]. Médecine Nucléaire 2008; 32: 46-50.
[6] Soulié M et al. Place de la chirurgie dans les tumeurs de la prostate à haut risque [The place of surgery in high-risk prostate cancers]. Cancer/Radiothérapie 2010;14: 493-9.
[7] TC Opinion on JEVTANA, 2012

According to the experts, just 10% of the 3700 patients exhibiting only symptomatic bone metastases have had a failure of the usual analgesic treatments and are eligible for treatment with METASTRON, i.e. about 370 patients a year.

Conclusion
The target population for METASTRON is of the order of 370 patients.

Very marginal use of this proprietary medicinal product has been observed; 45 vials were sold in 2012 and breaks in supply were reported in 2013.

013 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends continued inclusion on the list of medicines approved for hospital use "as an adjunct or alternative to external radiotherapy in the palliative treatment of pain associated with bone metastases secondary to prostate cancer in patients in whom hormone therapy has failed" and at the dosage in the Marketing Authorisation.