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TRANSPARENCY COMMITTEE
Opinion
1 October 2014

QUADRAMET 1.3 GBq/ml, solution for injection
1 glass vial of 15 ml (CIP: 34009 560 986 9 9)

Applicant: CIS bio international

INN	Samarium (^{153}Sm) lexidronam pentasodium
ATC code (2013)	V10BX02 (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 concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication concerned	"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. The presence of osteoblastic metastases which take up technetium (^{99m}Tc)-labelled bisphosphonates should be confirmed prior to therapy."

Actual Benefit	**Low**
Improvement in Actual Benefit	**The proprietary medicinal product QUADRAMET does not provide any improvement in actual benefit (IAB V, nonexistent) in the strategy for the management of painful osteoblastic skeletal metastases of various origins (mammary, pulmonary, prostatic).**
Therapeutic use	**When purely analgesic radioisotope treatment is considered for patients who have pain associated with bone metastases of prostate cancer which take up the substance on bone scan, QUADRAMET retains a benefit in hyperalgesic patients in whom hormone therapy has failed and whose pain is not controlled by the usual analgesics (opioids). Unlike METASTRON, its Marketing Authorisation is not limited to prostate cancer.** **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	**According to the experts, the population likely to derive particular benefit from QUADRAMET is between 370 and 420 patients.** **In practice, the number of patients treated is small (276 doses were sold in 2012 and 229 in 2013).**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	5 February 1998 (centralised procedure)
Prescribing and dispensing conditions /special status	List I Medicinal product reserved for hospital use Medicine for restricted medical prescription: QUADRAMET should be administered only by specialists in nuclear medicine and after full evaluation of the clinical case by doctors qualified in oncology

ATC Classification	2013	
	V	Various
	V10	Therapeutic radiopharmaceuticals
	V10B	Pain palliation (bone seeking agents)
	V10BX	Various pain palliation radiopharmaceuticals
	V10BX02	Samarium(^{153}Sm) lexidronam

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 QUADRAMET, solution for injection.

QUADRAMET is a radiopharmaceutical (a medicine containing a radioactive substance). It consists of radioactive samarium complexed with a tetraphosphonate chelator, ethylenediamine-tetramethylenephosphonate (EDTMP). It is the phosphonate EDTMP which has an affinity for bone and leads to uptake by the bony tissue, thus allowing samarium to exert its action. Samarium-153 **(**^{153}Sm) is a radioelement which emits both medium-energy beta particles and a gamma photon allowing scintigraphic images to be recorded.

It has been approved for hospital use since June 1998, its AB was rated as substantial and its therapeutic contribution was considered to be of the same order as that of METASTRON (Opinion of 22.04.1998), another radioisotope containing strontium (^{89}Sr) chloride. For the record, the Transparency Committee Opinion on METASTRON did not specify an IAB (Opinion of 8 July 1993).

276 doses of QUADRAMET were sold in France in 2012, 229 in 2013.

03 THERAPEUTIC INDICATION

“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. The presence of osteoblastic

metastases which take up technetium (^{99m}Tc)-labelled bisphosphonates should be confirmed prior to therapy."

04 Dosage

"QUADRAMET should be administered only by specialists in nuclear medicine and after full evaluation of the clinical case by doctors qualified in oncology.

Posology
The recommended dose of QUADRAMET is 37 MBq per kg body weight.
Paediatric population
QUADRAMET is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

Method of administration
QUADRAMET is to be administered by the slow intravenous route through an established intravenous line over a period of one minute. QUADRAMET should not be diluted before use.
In patients who respond to QUADRAMET, the beneficial effect on pain is generally observed within 1 week after treatment. The effect may persist for 4 weeks up to 4 months. Responder patients will be able to reduce their use of opioid analgesics.
Repeat administration of QUADRAMET should be based on the response to the first treatment and on the clinical symptoms, after a minimum interval of 8 weeks and subject to the recovery of satisfactory bone marrow function.
The data on the safety of repeated dosing are limited and based on compassionate use of the product."

05 Contraindications and warnings

5.1 Contraindications

- Hypersensitivity to the active substance (ethylenediaminetetramethylenephosphonate (EDTMP) or phosphonate derivatives) or to any of the excipients,
- In pregnant women,
- In patients having received chemotherapy or hemi-body external radiation therapy in a preceding period of 6 weeks.

QUADRAMET is used only as a palliative agent and should not be used concurrently with chemotherapy capable of aggravating myelotoxicity. It should not be used concurrently with other bisphosphonates if interference is shown on technetium (^{99m}Tc)-labelled bisphosphonate bone scans.

5.2 Special warnings and precautions for use
In the absence of clinical data, the injected activity should be adapted to renal function. Use of QUADRAMET is not recommended in patients with reduced haematopoiesis through impairment of bone marrow reserves due to previous treatments or to progression of the disease, unless the potential benefit of the treatment is considered to be greater than the risks involved.
Because of the potential myelotoxicity of QUADRAMET, haematological monitoring of patients should be carried out every week, from the second week after administration, for at least 8 weeks, or until recovery of adequate bone marrow function. Before injection, it is recommended that patients should be encouraged to drink (or receive by intravenous administration) at least 500 ml of fluids and, after injection, patients should be asked to urinate as often as possible, to reduce the dose absorbed by the bladder.

Since the elimination of QUADRAMET is rapid, precautions relating to the radioactivity eliminated in the urine are no longer necessary after 6-12 hours following injection. In patients with urinary incontinence, special precautions such as bladder catheterisation should be taken for 6 hours after administration to reduce the risks of contamination of clothing, bed linen and the patient's environment. Bladder catheterisation should be performed in patients with urinary obstruction. Urine should be collected for at least six (6) hours.
Radiopharmaceuticals may be used only by qualified persons who have obtained the appropriate national authorisation to use and handle radionuclides. This radiopharmaceutical may be received, used and administered only by authorised persons in approved departments. Its receipt, storage, use, transfer and disposal are subject to the regulations and the appropriate authorisations of the competent authorities.
Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

06 Therapeutic need

Unlike METASTRON, the indication in the Marketing Authorisation for QUADRAMET is not limited to the analgesic treatment of bone metastases of prostate cancer alone, but also covers various cancers.
More than 50% of patients with one of the 3 commonest cancers (lung, prostate, breast) develop bone metastases. These bone metastases cause numerous complications. Depending on their localisation and bone-marrow impact, they may be responsible for substantial morbidity, particularly bone pain, fractures, bone marrow compression or haematological complications associated with bone marrow 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.
Three radioisotopes are available; two of them (strontium ^{89}Sr and samarium ^{153}Sm-labelled diphosphonate) have Marketing Authorisation only in the treatment of pain associated with bone metastases; the Marketing Authorisation of radium dichloride (^{223}Ra) is not limited to the analgesic component, given its demonstrated favourable effect on overall survival.
Specifically in prostate cancer, abiraterone acetate (ZYTIGA), in combination with prednisone or prednisolone, has Marketing Authorisation in patients with metastatic prostate cancer limited to the bone and with few symptoms (the most intense pain score recorded within the last 24 hours < 3 on a VAS scale of 0-10), after failure of androgen suppression treatment and for whom chemotherapy is not yet clinically indicated.

07 Clinically relevant comparators

07.1 Medicinal products

Radiopharmaceutical proprietary medicinal products

Two other radioisotope medicines have an indication in bone metastases:

- limited to the analgesic component like QUADRAMET, METASTRON, strontium (^{89}Sr) chloride solution for injection, the effect of which on overall survival has not been demonstrated. The indication in its Marketing Authorisation is limited to prostate cancer.
- XOFIGO 1000 kBq/ml, solution for injection, radium (^{223}Ra) dichloride, 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 who have symptomatic bone metastases and no known soft tissue metastases (Opinion of 02.04.2014).

Name (INN) *Company*	Same TC* Yes / No	Indication	Marketing Authorisation	Date of Opinion
METASTRON, solution for injection, strontium (^{89}Sr) chloride GE HEALTHCARE SAS	Yes	"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."	24.03.1993	NA**
XOFIGO 1000 kBq/ml, solution for injection radium (^{223}Ra) dichloride BOEHRINGER INGELHEIM FRANCE	Yes	"Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases."	13.11.2013	02.04.2014

*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 patients with metastatic prostate cancer limited to the bone and with few symptoms (the 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

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

08 International information on the medicinal product

This proprietary medicinal product has Marketing Authorisation in 28 countries in the European Union and is reimbursed in Belgium, Italy and in France in the indication in its Marketing Authorisation .

09 Summary of previous assessments

Indication	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. The presence of osteoblastic metastases which take up technetium (^{99m}Tc)-labelled bisphosphonates should be confirmed prior to therapy.
Date of Opinion (reason for the request)	22 April 1998 (Inclusion on the list of medicines approved for hospital use)
Actual Benefit (wording)	Actual benefit Bone metastases are generally revealed by bone pain or by radiological signs. Most of the metastases originate from a cancer of the breast, prostate or lungs. The median survival of patients with these metastases is of the order of 5 months. QUADRAMET has demonstrated its efficacy in the treatment of pain from these metastases which take up technetium [^{99m}Tc]-labelled bisphosphonates. METASTRON is a treatment alternative, but its use is limited to the treatment of pain from bone metastases of prostatic origin. The role of QUADRAMET is important in the strategy for the management of pain from bone metastases.
Improvement in Actual Benefit (wording)	Improvement in actual benefit (IAB) QUADRAMET makes a therapeutic contribution of the same order as that of METASTRON in the strategy for the management of cancer patients for the analgesic treatment of bone metastases.
Target population (wording)	Cancer patients with painful bone metastases, the primary of which may be the breast, the prostate, the lungs or any other cancer for which an initial assessment of spread showed that bone metastases were taking up ^{99m}technetium-labelled bisphosphonates.

010 Analysis of available data

010.1 Efficacy

Reminder of the clinical studies in the initial dossier:
The Committee's conclusions in 1998 were as follows: "studies have shown the efficacy of this product in the treatment of pain from bone metastases in almost 400 patients.
In patients who respond to QUADRAMET, the beneficial effect on pain is generally observed within 1 week after treatment. The effect may persist for 4 weeks up to 4 months. Responder patients were observed to have reduced opiate use. Clinical studies have shown that the administration of QUADRAMET leads to the onset of leucopenia and thrombocytopenia: reduction of about 40-50% by comparison with baseline appearing between the 3rd and the 5th week after injection. The leucocyte and platelet counts generally return to the observed pre-treatment levels in 8 weeks. No trial has compared this proprietary medicinal product with METASTRON. However, the response rate with METASTRON is substantial, but the analgesic effect often does not appear until several weeks after administration of the treatment. Its use, as with QUADRAMET, is associated with bone marrow toxicity, but for longer."

Update of the clinical efficacy data
As part of the re-assessment of QUADRAMET, samarium-153, the company supplied tabular summaries and publications on open, non-randomised clinical studies, most of them of poor methodological quality; most were performed in small populations or have already been taken into account in the previous assessment, and consequently are not described here.
The dossier quotes data for the combination of QUADRAMET with docetaxel chemotherapy; according to its SPC, QUADRAMET should not be used concomitantly with chemotherapy that may aggravate myelotoxicity, so these data will not be taken into account.
A study comparing QUADRAMET with radioisotopes that do not have Marketing Authorisation in France (188Re-HEDP and 186Re-HEDP) was also included in the dossier but cannot be taken into account. A study comparing the effect of ^{153}Sm with that of pamidronic acid cannot be taken into account because it was performed in a small population of patients (18 in total). Other studies assessing the effect of QUADRAMET 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 assessment of the efficacy of QUADRAMET in the wording of the indication specified by the Marketing Authorisation , i.e. the treatment of pain associated with bone metastases.
Finally, a randomised study comparing the combination of samarium-153 + local radiotherapy with samarium-153 alone was added to the dossier but will not be described since QUADRAMET does not have Marketing Authorisation in combination with radiotherapy.

Overall, among the data supplied concerning the indication in its Marketing Authorisation , i.e. treatment of bone pain, just one relevant study can be used:

- study by Baczyk et al (2007)[1]

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,

[1] 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):245-250.

the patients were being treated with analgesics (NSAIDs and/or opioids), without a satisfactory response.
Only the results for prostate cancer (the only Marketing Authorisation indication for METASTRON) are presented. There was found to be no difference in analgesic efficacy 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 (range 0-100) 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.

010.2 Adverse effects

The company submitted the latest PSUR covering the period from 05 February 2010 to 04 February 2013, the analysis of which does not reveal any new safety signal with QUADRAMET.
The known potential adverse effects of QUADRAMET are qualitatively identical to those of METASTRON: a possible increase in pain (transient and improved by analgesics), bone marrow toxicity, the occurrence of thrombocytopenia and leucopenia, reduction in the platelet count.

010.3 Summary and discussion

In the Transparency Committee's assessment in 1998, the available data showed the efficacy of QUADRAMET, samarium-153, as analgesic treatment for metastatic bone pain.
Since that assessment, clinical studies of poor methodological quality, some performed in small populations and/or outside the scope of the wording of its indication in the Marketing Authorisation , or which have already been taken into account by the Committee in its previous assessment, have been published.

As part of this re-assessment, a single randomised clinical study was included. It compared samarium-153 with the other radioisotope available in France, strontium-89 (METASTRON), and did not show any difference in terms of analgesic efficacy between these 2 radioisotopes in the subgroup with prostate cancer.

Unlike with XOFIGO, the available data do not provide convincing evidence of the beneficial effect of QUADRAMET on survival.

No particular safety signal was observed. The known potential adverse effects of QUADRAMET are (qualitatively) identical to those of METASTRON: a possible increase in pain (transient and improved by analgesics), bone marrow toxicity, the occurrence of thrombocytopenia and leucopenia, reduction in the platelet count.

010.4 Planned studies

None.

011 Therapeutic use

When purely analgesic radioisotope treatment is considered in patients who have pain associated with bone metastases of prostate cancer that take up contrast in scintigraphy, QUADRAMET retains a benefit particularly in situations in which pain is difficult to control with opioid analgesics. It also has the advantage of having Marketing Authorisation in other types of cancer than prostate cancer.
Its role in therapeutic use could though be limited, given 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 QUADRAMET is 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 spinal cord compression.
◗ This proprietary medicinal product is intended as a specific non-curative treatment for painful osteoblastic bone metastases.
◗ Its analgesic efficacy was 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 cancer with symptomatic, osteoblastic metastases likely to receive QUADRAMET is moderate because of the substantial associated mortality.
Improving 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, QUADRAMET 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 interest 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.

Taking account of these points, the Committee considers that the actual benefit of QUADRAMET is <u>low</u> in the Marketing Authorisation indication, i.e. "relief of bone pain in patients with multiple painful osteoblastic metastases which take up technetium (^{99m}Tc)-labelled bisphosphonates on bone scan".

012.2 Improvement in actual benefit (IAB)

The proprietary medicinal product QUADRAMET does not provide any improvement in actual benefit (IAB V, nonexistent) in the strategy for the management of painful osteoblastic skeletal metastases of various origins (mammary, pulmonary, prostatic).

012.3 Target population[2]

According to the experts, the target population likely to derive benefit from treatment with QUADRAMET consists of patients with cancer of the prostate, lungs or breast, or any other cancer with symptomatic osteoblastic bone metastases that take up ^{99m}technetium-labelled bisphosphonates, in whom hormone therapy and the usual analgesic treatments have failed.

[2] Opinion on XGEVA of 11 April 2012

For prostate cancer:[3]

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

- patients initially diagnosed at metastatic stage;
- 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 Assessment 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 at the localised stage on diagnosis, progressing to a metastatic stage:
In these patients, the percentage of progression 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).[4] Based on the distribution of clinical stages T1 (27%) and T2 (58%) on diagnosis reported in the OPEPS study, the percentage of progression 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 at the locally advanced stage on diagnosis progressing to a metastatic stage:
Locally advanced tumours have a rate of progression to a metastatic stage of roughly 40% at five years.[5] 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.[6]

About 40% are said to have only symptomatic bone metastases, i.e. about 3700 patients a year. Of these, the proportion of patients with osteoblastic metastases is smaller; it is said to be 15%, i.e. about 550 patients, and the proportion in whom the usual analgesic treatments have failed and who are eligible for treatment with QUADRAMET is, according to the experts, 10%, i.e. 55 patients.

[3] Opinion on XOFIGO of 4 April 2014.
[4] Avancès C. Cancer de la prostate: la maladie localisée [Prostate cancer: the localised disease]. Médecine Nucléaire. 2008; 32: 46-50.
[5] Soulié M et al. Place de la chirurgie dans les tumeurs de la prostate à haut risque [Place of surgery in high-risk prostate tumours]. Cancer/Radiothérapie 2010;14: 493-9.
[6] TC Opinion on JEVTANA, 2012

For breast cancer

The metastatic stage at the outset accounts for 5-15% of cases, i.e. about 5250 new cases, and the metastatic stage after local spread accounts for 28% of cases, i.e. 14,700 cases.[7,8]

The proportion of patients with a bone localisation among the overall number of patients at the metastatic stage is estimated to be between 41 and 57% (data from Louis Harris, 2007).

The incidence of patients with breast cancer and bone metastases is estimated to be between 8000 and 11,400 patients. **That of patients with osteoblastic metastases undergoing treatment is lower, at between 1200 and 1700. Of these, according to the experts, only 10% have had a failure of the usual analgesic treatments and are eligible for treatment with QUADRAMET, i.e. between 120 and 170 patients.**

Other solid tumours, particularly lung cancer

The incidence of patients with a solid tumour, apart from breast and prostate cancer, and falling within the indication is estimated to be about 13,000 patients, including 8000 that are lung cancers (data from Louis Harris, 2007). **Of these, the proportion of patients with osteoblastic metastases is smaller, with not more than 1950 patients.**

Of these, according to the experts, only 10% have had failure of the usual analgesic treatments and are eligible for treatment with QUADRAMET, i.e. at most 195 patients.

Conclusion:

According to the experts, the population likely to derive benefit from treatment with QUADRAMET is at most between 370 and 420 patients.

In practice, marginal use of this proprietary medicinal product is observed; 276 doses were sold in 2012 and 229 in 2013.

013 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication "For the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases that take up technetium (^{99m}Tc)-labelled bisphosphonates on bone scan" and at the dosage in the Marketing Authorisation .

[7] Investigation by the French Federation of Cancer Centres (FNCLCC)
[8] FRANCIM