QUADRAMET®

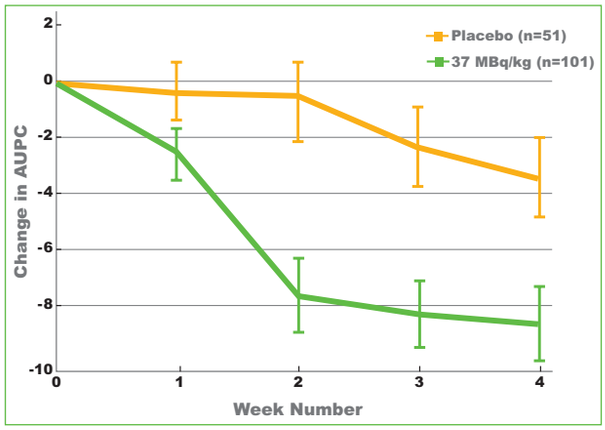
Samarium [^{153}Sm] Lexidronam injection
Palliative metabolic radiotherapy

A step forward... for a better quality of life

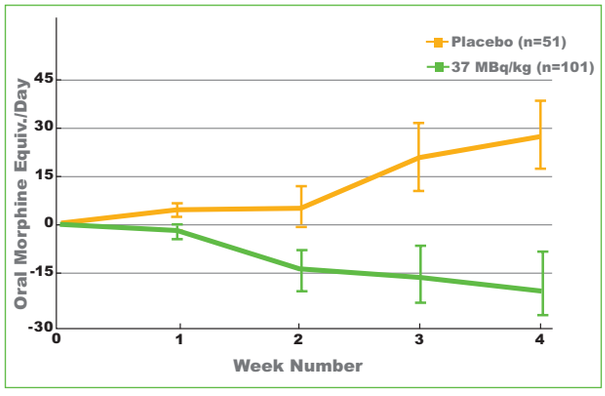
Quadramet®
Effective Pain Reduction

Fast and effective with short physical half-life (1.9 days)
A rapid delivery of radiation dose

- Several international multicenter studies prove **pain reduction in more than 70 % of patients** after Quadramet® administration.(1, 2, 3, 4, 5)
- **A significant reduction of pain intensity** occurs within one week – and with more than 16 weeks duration.(3, 4)
- After Quadramet® administration **the use of opioids,** which is often accompanied by adverse events **may be reduced.**(3, 4)



Area Under the Pain Curve (AUPC) derived from daily patient Visual Analogue Scale Scores (VAS): significant decrease compared with placebo (p = 0.034) (4)



Opioid Analgesic Use: significant decrease compared with placebo (p = 0.041) (4)

with predictable and moderate undesirable effects

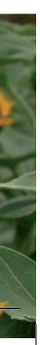
- Fast and nearly exclusive renal elimination **reducing the whole body irradiation.**

- **Grade 2** myelotoxicity in 85 to 90 % of patients [2]
  Grade 3 to 4 myelotoxicity in 10 to 15 % of patients [2].

- **Transient effect on the bone marrow** due to individual, weight-dependent dosage and very advantageous radiation-properties of Quadramet® [2].

- Usable **between two cycles of chemotherapy,** after normalisation of the blood count (see SPC).

- **Registered for the treatment of all painful osteoblastic bone metastases which take up technetium [^{99m}Tc] - labelled biphosphonates on bone scan,** independently from the primary tumor.

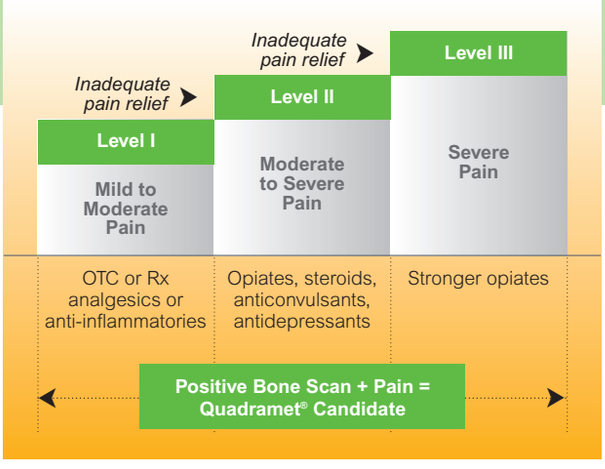


Quadramet®
For the treatment of painful osteoblastic metastases

The use of Quadramet® from the early stage of pain leads to:

- **a significant pain reduction** ($p < 0.034$)[3] with a high efficacy and low undesirable effects,
- **less adverse** reactions compared to the use of opioids,
- the **reduction of the daily dosage of analgesics,**
- the **improvement of long lasting therapeutical options.**

Better mobility and improvement of quality of life for the patients.



WHO-Scheme
for the therapy of tumour-associated pain and the possible inclusion of Quadramet®.

in co-operation with nuclear medicine

- **The application of the therapy is done by a nuclear physician** with customised dosage adjusted to the weight of the patient.
- **A direct bone scintigraphy** is possible.
- The treatment can be done on **out-patient** basis.
- **The treatment is repeatable** at minimum 8 weeks interval (see SPC).
- **The conventional treatment of the patient** is continued by the referrer.

[1] Collins C., et al. Samarium 153 EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. *J Nucl Med*. 1993; 34: 1839-1844.

[2] Resche I, et al. A dose-controlled study of ^{153}Sm-EDTMP in the treatment of patients with painful bone metastases. *European Journal of Cancer.* 1997; 33 (10): 1583-1591.

[3] Serafini AN, et al. Palliation of pain associated with metastatic bone cancer using Samarium ^{153}Sm Lexidronam: a double blind placebo-controlled clinical trial. *J Clin Onc.* 1998; 16 (4): 1574-1581.

[4] Sartor O., et al for the Quadramet ^{424}Sm10/11 study group. Samarium-153-Lexidronam complex for treatment of painful bone metastases in Hormone Refractory Prostate Cancer. *Urology.* 2004; 63: 940-945.

[5] Maini C.L. et al. ^{153}Sm-EDTMP for bone pain palliation in skeletal metastases. *Eur J Nucl Med Mol Imaging.* 2004; 31(1): 171-178.

[6] Lewington V.J. Symposium of interventional nuclear medicine. A practical guide to targeted therapy for bone pain palliation. *N M C.* 2002; 23: 833-836.

A typical Quadramet®-patient

- **Patient:**
  male, 67 years old, 78 kg

- **Medical history:**
  prostate carcinoma since 6 years, prostatectomy; bone metastases known since 1 year; increase of bone pain despite therapy with analgesics, marginal increase of PSA

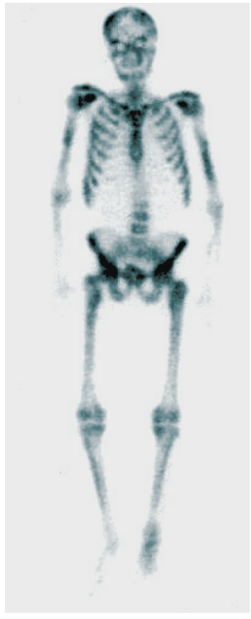
- **Personal data:**
  married, retired, 2 grown-up children

- **Premedication:**
  opioids, NSAR-analgesics

- **Adverse events:**
  sleeping disturbances, constipation, reduced vigilance

- **Therapy with Quadramet®:**
  injection of 2.9 GBq (78 mCi) Samarium [^{153}Sm] Lexidronam

- **Therapeutic effects:**
  after 3 days short-lasting increase of pain (flare-phenomenon), after 8 days significant reduction of pain;
  after 2 weeks withdrawal of opioids, continuation with NSAR-analgesics;
  after 5 months pain recurrence and repetition of Quadramet® treatment;
  no further increase of PSA since the first injection



A typical Quadramet®-patient

- **Patient:**
  female, 47 years old, 62 kg

- **Medical history:**
  breast carcinoma since 5 years (T2 N1 M0), segmental resection and axillary lymphnode resection, cytostatic treatment, external beam radiation, bone metastases and local recurrence, positive ER-status, insufficient pain reduction

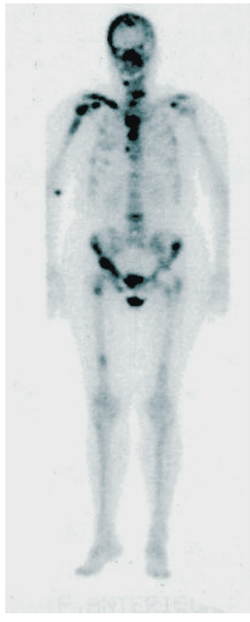
- **Personal data:**
  married, house-wife, 2 children attending high school

- **Premedication:**
  tamoxifen, opioids, NSAR-analgesics, bisphosphonates

- **Adverse events:**
  constipation, transient vertigo and vomiting

- **Therapy with Quadramet®:**
  injection of 2.3 GBq (62 mCi) Samarium [^{153}Sm] Lexidronam

- **Therapeutic effects:**
  after 6 days pain reduction, termination of opioids, 7 days later termination of NSAR-analgesics, full participation in daily duties;
  after 4 months still pain free



Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

QUADRAMET, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 1.3 GBq Samarium [^{153}Sm] lexidronam pentasodium at the reference date (corresponding to 20 to 46 µg/ml of samarium per vial).
Samarium specific activity is approximately 28 – 65 MBq/µg of samarium.
Each vial contains 2-4 GBq at the reference date.
Samarium-153 emits both medium-energy beta particles and an imageable gamma photon, and has a period of 46.3 hours (1.93 days).
The primary radiation emissions of samarium-153 are shown in Table 1.

TABLE 1 : SAMARIUM-153 PRINCIPAL RADIATION EMISSION DATA

Radiation	Energy (keV)*	Abundance
Beta -	640	30%
Beta -	710	50%
Beta -	810	20%
Gamma	103	29%

** Maximum energies are listed for the beta emissions, the average beta particle energy is 233 keV.*

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to light amber solution with pH ranging between 7.0 and 8.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

QUADRAMET is indicated for the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases which take up technetium [^{99m}Tc]-labelled biphosphonates on bone scan.
The presence of osteoblastic metastases which take up technetium [^{99m}Tc]-labelled biphosphonates should be confirmed prior to therapy.

4.2 Posology and method of administration

QUADRAMET should only be administered by physicians experienced in the use of radiopharmaceuticals and after full oncological evaluation of the patient by qualified physicians.
The recommended dose of QUADRAMET is 37 MBq per kg body weight and is to be administered by slow intravenous route through an established intravenous line over a period of one minute. QUADRAMET should not be diluted before use.
Patients who respond to QUADRAMET generally experience the onset of pain relief within 1 week after treatment. Relief of pain may persist for 4 weeks up to 4 months. Patients who experience a reduction in pain may be encouraged to decrease their use of opioid analgesics.
Repeat administration of QUADRAMET should be based on an individual patient's response to prior treatment and on clinical symptoms. A minimum interval of 8 weeks should be respected, subject to recovery of adequate bone marrow function.
The data on the safety of repeated dosing are limited and based on compassionate use of the product.
QUADRAMET is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contra-indications

QUADRAMET is contra-indicated:

- Hypersensitivity to the active substance (ethylenediaminetetramethylenephosphonate (EDTMP) or similar phosphonates) or to any of the excipients.
- in pregnant women (See section 4.6).
- 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 myelotoxic chemotherapy as this may enhance myelotoxicity.
It should not be used concurrently with other biphosphonates if an interference is shown on the technetium [^{99m}Tc]-labelled biphosphonate bone scans.

4.4 Special warnings and special precautions for use

In absence of clinical data, the injected activity should be adapted to the renal function.
Use of QUADRAMET in patients with evidence of compromised bone marrow reserve from previous therapy or disease involvement is not recommended unless the potential benefit of the treatment outweighs its risks.
Because of potential bone marrow suppression after administration, blood counts should be monitored weekly for at least 8 weeks, beginning 2 weeks after administration of QUADRAMET, or until recovery of adequate bone marrow function.
The patient should be encouraged to ingest (or receive by intravenous administration) a minimum of 500 ml of fluids prior to injection and should be encouraged to void as often as possible after injection to minimise radiation exposure to the bladder.
The clearance of QUADRAMET being rapid, the precautions relating to the excreted urinary radioactivity need not be taken after 6-12 hours following administration.
Special precautions, such as bladder catheterisation, should be taken during six hours following administration to incontinent patients to minimise the risk of radioactive contamination of clothing, bed linen, and the patient's environment. For the other patients the urine should be collected for at least six (6) hours.
Bladder catheterisation should be undertaken in patients with urinary obstruction.
Radiopharmaceuticals may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and the appropriate licences of the local competent official organisations. Radiopharmaceuticals should be prepared by the user 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.

4.5 Interaction with other medicinal products and other forms of interaction

Because of the potential for additive effects on bone marrow, the treatment should not be given concurrently with chemotherapy or external beam radiation therapy. QUADRAMET may be given subsequent to either of these treatments after allowing for adequate marrow recovery..

4.6 Pregnancy and lactation

QUADRAMET is contra-indicated (see 4.3) in pregnancy. The possibility of pregnancy must strictly be ruled out. Women of childbearing potential have to use effective contraception during the treatment and the whole period of follow-up.
There are no available clinical data relating to the excretion of QUADRAMET in human milk. If therefore QUADRAMET administration is deemed necessary, formula feeding should be substituted for breast-feeding and the expressed feeds discarded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Decreases in white blood cell and platelet counts and anaemia were observed in patients receiving QUADRAMET.
In clinical trials white blood cell and platelet counts decreased to a nadir of approximately 40% to 50% of baseline 3 to 5 weeks after a dose, and generally returned to pre-treatment levels by 8 weeks post treatment.
The few patients who experienced Grade 3 or 4 hematopoietic toxicity usually either had a history of recent external beam radiation therapy or chemotherapy or had rapidly progressive disease with probable bone marrow involvement.
Postmarketing reports of thrombocytopenia have included isolated reports of intracranial haemorrhage, and cases in which the outcome was fatal.
A small number of patients have reported a transient increase in bone pain shortly after injection (flare reaction). This is usually mild and self-limiting and occurs within 72 hours of injection. Such reactions are usually responsive to analgesics.
Adverse drug reactions such as nausea, vomiting, diarrhoea and sweating were reported.
Hypersensitivity reactions including rare cases of anaphylactic reaction have been reported after QUADRAMET administration.
A few patients experienced cord/root compressions, disseminated intravascular coagulation and cerebrovascular accidents. The occurrence of these events may be linked to the patients' disease evolution. When there are spinal metastases at the cervico-dorsal level, an increased risk of spinal cord compression cannot be excluded.
The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself.

4.9 Overdose

The product should only be administered by qualified personnel in authorised settings. The possibility of pharmacological overdose is therefore remote.
The risks to be expected are associated with the inadvertent administration of excess radioactivity. Radiation dose to the body can be limited by promoting a diuresis and frequent voiding of urine.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Various pain palliation radiopharmaceuticals.

ATC Code: V10BX02
QUADRAMET has an affinity for skeletal tissue and concentrates in areas of bone turnover in intimate association with hydroxyapatite; studies in rats have demonstrated that QUADRAMET is cleared rapidly from the blood and localises to growing areas of bone matrix, specifically the layer of osteoid undergoing mineralisation.
In clinical studies employing planar imaging techniques, QUADRAMET accumulates with a lesion-to-normal bone ratio of approximately 5 and a lesion-to-soft tissue ratio of approximately 6. Thus, areas of metastatic involvement can accumulate significantly greater amounts of QUADRAMET than surrounding normal bone.

5.2 Pharmacokinetic properties

In patients, QUADRAMET is rapidly cleared from the blood. Thirty minutes after injection of the agent to 22 patients, only 9.6 ± 2.8 % of the administered activity remained in plasma. At 4 and 24 hours, plasma radioactivity had decreased from 1.3 ± 0.7 % to 0.05 ± 0.03 %. Urinary excretion occurred predominantly during the first 4 hours (30.3 ± 13.5 %). At 12 hours, 35.3 ± 13.6 % of the administered activity had been excreted into the urine. Analysis of urine samples found the radioactivity to be present as the intact complex. Less urinary excretion occurred in patients who had extensive bony metastases, regardless of the amount of radiopharmaceutical administered. Total skeletal uptake of QUADRAMET in studies of 453 patients with a variety of primary malignancies was 65.5 ± 15.5 % of the administered activity. A positive correlation was found between skeletal uptake and the number of metastatic sites. In contrast, skeletal uptake was inversely proportional to plasma radioactivity at 30 minutes.

5.3 Preclinical safety data

The radiolysis products of Sm-EDTMP showed a renal toxicity in rats and dogs with a no effect level of 2.5 mg/kg.
Repeated dose administration of samarium [^{153}Sm]-EDTMP to dogs indicated a slightly longer time for depressed bone marrow and peripheral haematological parameters to recover when compared to recovery following only single dose administration.
Radioactive Sm-EDTMP has not been tested for mutagenicity/carcinogenicity but due to the radiation dose resulting from therapeutic exposure it should be regarded as presenting a genotoxic/carcinogenic risk.
Non-radioactive Sm-EDTMP showed no mutagenic potential in a battery of *in vivo* and *in vitro* tests. The same results were observed for Sm-EDTMP enriched with radiolysis degradants.
In a carcinogenic potential study of EDTMP, osteosarcomas occurred in rats at high doses. In the absence of genotoxic properties, these effects can be assigned to the EDTMP chelatant properties leading to osseous metabolism disturbances.
No studies have been performed to assess the effect of QUADRAMET on reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Total EDTMP (as EDTMP.H_2O)
Calcium-EDTMP sodium salt (as Ca)
Total sodium (as Na)
Water for Injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with the other medicinal products.

6.3 Shelf-life

1 day from the activity reference time stated on the label.
Use within 6 hours of thawing. After thawing, do not freeze again.

6.4 Special precautions for storage

QUADRAMET is delivered frozen in dry ice.
Store in a freezer at -10°C to -20°C in the original package.
Storage procedures should be in accordance with local regulations for radioactive substances.

6.5 Nature and content of container

15 ml colourless European Pharmacopoeia Type I drawn glass vial closed with Teflon-coated chlorobutyl/natural rubber stopper and aluminium flip-off overseal.
Each vial contains 1.5 ml (2 GBq at calibration) to 3.1 ml (4 GBq at calibration) of solution for injection.

6.6 Special precautions for disposal and other handling

The administration of radiopharmaceuticals creates risks to other persons from external radiation or contamination from spills of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.
Any unused product or waste material should be disposed of in accordance with local requirements.
(See section 12, for detailed instructions of product preparation)

7. MARKETING AUTHORISATION HOLDER

CIS bio international - Boîte Postale 32 - F-91192 GIF-SUR-YVETTE Cedex - FRANCE

8. MARKETING AUTHORISATION NUMBER

EU/1/97/057/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of the first authorisation: 05.02.1998
Date of the last renewal: 05.02.2008

10. DATE OF REVISION OF THE TEXT

06/2008

11. DOSIMETRY

The estimated absorbed radiation doses to an average adult patient from an intravenous injection of QUADRAMET are shown in Table 2. The dosimetry estimates were based on clinical biodistribution studies using methods developed for radiation dose calculations by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine.
Because QUADRAMET is excreted in the urine, radiation exposure was based on a urinary voiding interval of 4.8 hours. Radiation dose estimates for bone and marrow assume that radioactivity is deposited on bone surfaces, in accordance with autoradiograms of bone samples taken from patients who received QUADRAMET.
Radiation dose to specific organs, which may not be the target organ of therapy, may be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information:

TABLE 2 : RADIATION ABSORBED DOSES

Organ	Absorbed dose per injected activity (mGy/MBq)	Organ	Absorbed dose per injected activity (mGy/MBq)
Adrenals	0.009	Ovaries	0.008
Brain	0.011	Pancreas	0.005
Chest	0.003	Red marrow	1.54
Gallbladder	0.004	Bone surfaces	6.76
Ascending colon wall	0.005	Skin	0.004
Descending colon wall	0.010	Spleen	0.004
Small intestine	0.006	Stomach	0.004
Myocardial wall	0.005	Testes	0.005
Kidneys	0.018	Thymus	0.004
Liver	0.005	Thyroid	0.007
Lungs	0.008	Urinary bladder wall	0.973
Muscle	0.007	Uterus	0.011
	Effective dose (mSv/MBq)	**0.307**	

For this product the effective dose resulting from an injected activity of 2590 MBq is 796 mSv.
For an administered activity of 2590 MBq, the typical radiation dose to the target organ, skeletal metastases, is 86.5 Gy and the typical radiation doses to the critical organs are: normal bone surfaces 17.5 Gy, red marrow 4.0 Gy, urinary bladder wall 2.5 Gy, kidneys 0.047 Gy and ovaries 0.021 Gy.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Allow the product to thaw at room temperature before administration.
The solution for injection should be visually inspected before use. It should be clear without particles. The operator should be careful to protect the eyes while inspecting the solution for clarity.
The activity should be measured by a dose calibrator immediately before administration. Verification of the dose to be administered and patient identification are necessary prior to administration of QUADRAMET.
For radiation safety reasons, the patient should be treated in a facility with the appropriate agreement for the therapeutic use of radioactive non-sealed sources. He/she will be released when exposure rates comply with the limits prescribed by the regulations in force.
Any unused product or waste material should be disposed of in accordance with local requirements.

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

QUADRAMET®

Samarium [^{153}Sm] Lexidronam injection

A step forward...
for a better quality of life

- Systemic palliative therapy for all painful osteoblastic bone metastases which take up technetium [^{99m}Tc] - labelled biphosphonates on bone scan, whatever is the primary tumour
- Efficacy proved according to evidence-based medicine(6)
- Customised dose adjusted to patient's weight
- More than 70% response rate in prostate and breast cancer
- Quick onset of pain relief (1 week)
- More than 16 weeks duration of pain relief
- High and specific bone lesion uptake and minimal irradiation effects
- Transient effect on the bone marrow(2)
- Treatment repeatable at minimum 8 week interval
- Out-patient treatment possible
- Possible direct bone scintigraphy

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IBA delivers solutions of unprecedented precision in the fields of cancer diagnosis and therapy. The company also offers sterilization and ionization solutions to improve the hygiene and safety of everyday life.

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