

# **EANM procedure guideline for treatment of refractory metastatic bone pain**

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## **Abstract**

Bone pain is a common symptom of metastatic disease in cancer, experienced, with various intensity, by about 30% of cancer patients, during the development of their disease, up to 60-90% in the latest phases. In addition to other therapies, such as analgesics, bisphosphonates, chemotherapy and hormonal therapy, also bone-seeking radiopharmaceuticals are used for the palliation of pain from bone metastases. Substantial advantages of bone palliation radionuclide therapy include the ability to treat simultaneously multiple sites of disease, the ease of administration, the repeatability, and the potential integration with other treatments, such as chemotherapy agents, external-beam radiotherapy and bisphosphonates.

The Therapy, Oncology and Dosimetry Committees have worked together in order to revise the EANM guidelines on the use of bone-seeking radiopharmaceuticals. The purpose of this guideline is to assist the nuclear medicine physician in treating and managing patients undergoing to such treatment.

Keywords Guidelines. Nuclear medicine. Bone palliation.  $^{89}\text{Sr}$ .  $^{153}\text{Sm}$ -lexidronam.  $^{186}\text{Re}$ -etidronate.

## **I. Purpose**

The purpose of this guideline is to assist nuclear medicine practitioners in

1. Evaluating patients who might be candidates for treatment using  $^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam [ $^{153}\text{Sm}$ -EDTMP] or  $^{186}\text{Re}$ -etidronate [ $^{186}\text{Re}$ -HEDP] to palliate refractory, metastatic bone pain.
2. Providing information for performing these treatments.
3. Understanding and evaluating the consequences of therapy.

## **II. Background Information and Definitions**

### **A. Definitions**

1. Metastatic bone pain in this context means bone pain arising from secondary skeletal malignancy.

2. Treatment refractory means resistance to alternative treatments such as conventional analgesics, bisphosphonates, anti-tumour therapy [chemotherapy or hormone manipulation] or multisite symptoms not easily controlled by external beam radiotherapy or surgery.
3. Therapy in this context means the intravenous administration of  $^{89}\text{Sr}$ -chloride in aqueous solution, *or*  $^{153}\text{Sm}$ -lexidronam [ $^{153}\text{Sm}$ -ethylene-diamine-tetramethylene-phosphonate] (EDTMP), *or*  $^{186}\text{Re}$ -etidronate [ $^{186}\text{Re}$ -hydroxyethylidene-diphosphonate] (HEDP).
4. Osteoblastic means focal increased skeletal metabolic activity, namely sclerosis, caused by osseous reaction to bone metastases, as evidenced by increased activity on bone scintigraphy. Osteolytic means focal areas of bone destruction caused by the action of osteoclasts. A mixed pattern, however, is common in many lesions.

## B. Background

Intravenous injection of  $^{89}\text{Sr}$ -chloride,  $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate is approved in Europe for the treatment of bone pain due to osteoblastic metastases or mixed osteoblastic lesions. Radiopharmaceutical's approval for the clinical use may vary in different Countries.

1.  $^{89}\text{Sr}$  emits a beta particle with maximum energy 1.46 MeV, mean energy 0.58 MeV, average soft-tissue range 2.4 mm and 0.01% abundant gamma emission with a 0.91 MeV photo peak. The physical half-life is 50.5 days.
2.  $^{153}\text{Sm}$  emits a beta particle with maximum energy 0.81 MeV, mean energy 0.23 MeV, average soft-tissue range 0.6 mm and a 28% abundant, 0.103 MeV gamma emission. The physical half-life is 1.9 days.
3.  $^{186}\text{Re}$  emits a beta particle with maximum energy 1.07 MeV, mean energy 0.349 MeV, average soft-tissue range 1.1 mm and a 9% abundant gamma emission with a photo peak of 0.137 MeV. The physical half-life is 3.7 days.

## III. **Indications**

$^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate are indicated for the treatment of bone pain due to skeletal metastases involving more than one site associated with an osteoblastic response on bone scintigraphy.

### Contraindications:

#### *Absolute:*

Pregnancy; breastfeeding.

#### Relative:

The radiopharmaceuticals are not recommended for women of childbearing age.

Low blood cell counts:

1. Haemoglobin  $< 90 \text{ g l}^{-1}$
2. Total white cell count  $< 3.5 \times 10^9 \text{ l}^{-1}$
3. Platelet count  $< 100 \times 10^9 \text{ l}^{-1}$

Rapidly deteriorating renal function: GFR  $< 30 \text{ ml/min}$ .

Safety and toxicity of treatment in patients with renal insufficiency has not been thoroughly investigated. However, an increase of myelosuppressive toxicity is expected because of the impairment of renal excretion. It is therefore advised to lower the administered dose by 50% in patients with creatinine clearance < 50 mL/min (according to the Cockcroft and Gault formula\*). <sup>153</sup>Sm-lexidronam or <sup>186</sup>Re-etidronate is the treatment of choice. Repeated treatment in the case of acceptable toxicity must be considered after 8 weeks.

\* Cockcroft and Gault formula for creatinine clearance in mL/min. = [(140 – age) x weight (kg) x C] / (plasma creatinine x 0.814), in which C = 1 if male, C=0.85 if female. Plasma creatinine in umol/L.

<sup>89</sup>Sr, <sup>153</sup>Sm-lexidronam and <sup>186</sup>Re-etidronate have no place in the management of acute spinal cord compression or in treating pathological fractures. Metastases at risk of such complications should be appropriately evaluated on the basis of clinical and neurological symptoms, examination and, if necessary, radiology. In particularly selected cases, “chronic” spinal cord compression can be evaluated for radionuclide therapy, together with corticosteroid administration and a careful clinical observation.

## **IV. Procedure**

### **A. Facility and personnel**

The facilities required will depend on national legislation for the emission of pure beta and beta-gamma emitting therapy agents. If in-patient treatment is required by national legislation, this should take place in an approved facility with appropriately shielded rooms and en-suite bathroom facilities.

The facility in which treatment is administered must have appropriate personnel, radiation safety equipment, procedures available for waste handling and disposal, handling of contamination, monitoring personnel for accidental contamination and controlling contamination spread.

The administration of <sup>89</sup>Sr, <sup>153</sup>Sm-lexidronam or <sup>186</sup>Re-etidronate should be undertaken by appropriately trained medical staff with supporting physics and nursing staff.

Physicians responsible for treating patients should have an understanding of the clinical pathophysiology and natural history of the disease processes; should be familiar with other forms of therapy; should be able to liaise closely with other physicians involved in managing the patient.

Clinicians involved in unsealed source therapy must be knowledgeable about and compliant with all applicable national and local legislation and regulations.

### **B. Patient Preparation and Data required**

Patients considered for <sup>89</sup>Sr, <sup>153</sup>Sm-lexidronam or <sup>186</sup>Re-etidronate therapy will have failed conventional analgesics, bisphosphonates and anti-tumour therapy [chemotherapy, hormone manipulation]. Pain will usually limit normal activities and/or require regular analgesics.

Patients will have undergone recent [within 8 weeks or less] bone scintigraphy documenting increased osteoblastic activity at painful sites. Radiographs demonstrating osteosclerotic lesions are inadequate, as increased bone density does not always result in increased uptake on radionuclide imaging. Abnormalities on bone scintigraphy must be correlated with

appropriate physical examination to exclude other causes of chronic pain, which would be unlikely to respond to treatment using bone-seeking radiopharmaceuticals. Neurogenic pain and pathological fracture should be specifically excluded.

Treatment can be safely combined with local field external beam radiotherapy. The use of wide field [hemi-body] radiotherapy within 3 months of  $^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam or  $^{186}\text{Re}$ -etidronate administration is likely to result in increased myelosuppression and is relatively contraindicated. Long-acting myelosuppressive chemotherapy should be discontinued at least 4 weeks *before* administration of  $^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam or  $^{186}\text{Re}$ -etidronate and withheld for 6–12 weeks post therapy to avoid concomitant myelosuppression.

A full haematological and biochemical profile should be obtained within 7 days of proposed treatment. Recommended reference levels are listed in III.

Disseminated intravascular coagulation (DIC) may be a risk factor for severe thrombocytopenia post-therapy. It may be appropriate to perform pre treatment clotting studies to identify patients with subclinical DIC.

There are conflicting data as to whether bisphosphonates inhibit the uptake of radiolabeled phosphonates in bone metastases. This discussion is based on the hypothesis that as both drugs interact at the hydroxyapatite crystal surface of the skeleton, competition might exist for uptake by bone. At present, there is no evidence of competition between bisphosphonates and  $^{153}\text{Sm}$ -lexidronam,  $^{186}\text{Re}$ -etidronate or, particularly,  $^{89}\text{Sr}$ . Thus, they may therefore be used concomitantly.

$^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam or  $^{186}\text{Re}$ -etidronate therapy are inappropriate for patients with a life expectancy of less than 4 weeks.

### C. Patient Information and Instruction

Patients should receive both written and verbal information about the procedure before receiving therapy. Informed written consent must be obtained from the patient.

Patients should be told that 60 - 80 % of patients benefit from  $^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam or  $^{186}\text{Re}$ -etidronate therapy.

The patient should understand that  $^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam or  $^{186}\text{Re}$ -etidronate are palliative treatments and will not cure metastatic cancer.

Patients should be warned of the risk of temporary increase in bone pain [pain flare].

The patient should be told that pain reduction is unlikely within the first week, more probable in the second week and could occur as late as 4 weeks or longer after injection. Patients should continue prescribed analgesics until bone pain improves, and receive advice regarding subsequent analgesic dose reduction, where appropriate.

### D. Administration

$^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate are supplied in solution for use at room temperature.  $^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate should be administered by slow [ $^{89}\text{Sr}$ ] or bolus [ $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate] injection via an indwelling

intravenous butterfly or cannula followed by 0.9% saline flush. Care should be taken to avoid extravasation of the radiopharmaceutical.

Recommended administered activities are as follow:

- $^{89}\text{Sr}$  : 150 MBq
- $^{153}\text{Sm}$ -lexidronam: 37 MBq/kg
- $^{186}\text{Re}$ -etidronate : 1295 MBq

Retreatment can be effective and safe, provided that haematological parameters are fully recovered. This is recommended by the manufacturer at a minimum interval of 8 weeks for  $^{153}\text{Sm}$ -lexidronam, 6-8 weeks for  $^{186}\text{Re}$ -etidronate or 12 weeks for  $^{89}\text{Sr}$ .

Important differences between the radiopharmaceuticals are radiation half-life, energy of gamma-emission and beta-emission. These differences determine both the clinical benefit and the side-effects. Although no clear difference in treatment response between  $^{89}\text{Sr}$ ,  $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate was reported, differences in onset of response, duration of response and toxicity do exist. The onset of response is rapid after treatment with short-lived isotopes (i.e.  $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate). After treatment with long-lived isotopes ( $^{89}\text{Sr}$ ), the onset is prolonged for a few weeks. The duration of response, on the other hand, is longer for long-lived radioisotopes than for short-lived isotopes.

Patients with progressive disease and pain, for whom rapid relief is warranted, are best treated with short-lived isotopes. Relief will be quick and toxicity acceptable. If needed, patients can be treated multiple times with an interval of several months. Patients with a somewhat better prognosis and better clinical condition, for whom treatment of pain with radioisotopes is indicated, may be treated with long-lived isotopes. The duration of response will be longer. However, care must be taken for myelosuppressive toxicity.

Because multiple phase I/II studies focussing on the combination of chemotherapy and bone seeking radiopharmaceuticals are currently being performed, the different physical properties and toxicity profile of each radiopharmaceutical will become more important. This will probably prove to be most advantageous for short-lived isotopes.

#### E. Precautions, follow-up and side-effects

The treating clinician must advise the patient on reducing unnecessary radiation exposure to family members and the public.

Following treatment, patients should avoid pregnancy for at least 6 months after  $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate, and even longer for  $^{89}\text{Sr}$ . In reality, it is unlikely that women of childbearing age will be eligible for this therapy.

Urinary radiopharmaceutical excretion is of particular concern during the first 2-3 days post administration, particularly for  $^{89}\text{Sr}$ . Urinary excretion of  $^{186}\text{Re}$ -etidronate takes place mostly during the first 24 hours after administration. For  $^{153}\text{Sm}$ -lexidronam, it is nearly completed after the first 8-12 hours after administration. Patients should be advised to observe rigorous hygiene in order to avoid contaminating groups at risk using the same toilet facility. Patients should be warned to avoid soiling underclothing or areas around toilet bowls for 1 week post injection and that significantly soiled clothing should be washed separately. A double toilet flush is recommended after urination. Patients should wash their hands after urination. If

contaminated with urine, patients should wash their hands abundantly with warm water, without scrubbing.

Because urinary excretion of  $^{153}\text{Sm}$ -lexidronam and  $^{186}\text{Re}$ -etidronate is fast and takes place predominantly during the first 8-12 hours after injection, special caution for urinary contamination should be taken during this first period.

Incontinent patients should be catheterized before radiopharmaceutical administration for radioprotection of relatives and/or caring personnel. The catheter should remain in place for an appropriate period of time ( $^{89}\text{Sr}$ : 4 days,  $^{186}\text{Re}$ -etidronate: 2-3 days,  $^{153}\text{Sm}$ -lexidronam: 24 hours). Catheter bags should be emptied frequently. Gloves should be worn by staff caring for catheterized patients.

If in-patient treatment is required, nursing personnel must be instructed in radiation safety. Any significant medical conditions should be noted and contingency plans made in case radiation precautions must be breached for a medical emergency. Concern about radiation exposure should not interfere with the prompt appropriate medical treatment of the patient.

Periodical haematological monitoring may be useful up to 6 weeks post therapy ( $^{153}\text{Sm}$ -lexidronam,  $^{186}\text{Re}$ -etidronate) to exclude significant myelosuppression in high-risk patients. After treatment with  $^{89}\text{Sr}$  longer follow-up is necessary because of prolonged myelosuppressive toxicity (12-16 weeks).

Post therapy scintigraphy may be of value to clarify tumour extent and to perform dosimetry calculations.

#### *Side Effects:*

Calcium-like flushing sensation: described with the use of  $^{89}\text{Sr}$ , related to quick infusion (< 30 sec.).

“Flare” phenomena: increase of pain symptoms, in about 10% of the patients, usually within 72 hours, typically transient, usually mild and self-limiting, and usually responding to standard analgesics.

When cervico-dorsal spinal metastases are present, an increase rate of spinal cord compression is possible. Prophylactic corticosteroids may be considered according to local protocols.

A decrease of thrombocytes and leucocytes count in peripheral blood, as a result of myelosuppression, is frequently observed and has a nadir of 3-5 weeks ( $^{153}\text{Sm}$ -lexidronam,  $^{186}\text{Re}$ -etidronate) or 12-16 weeks ( $^{89}\text{Sr}$ ). The occurrence of grade 3 or 4 toxicity is dependent on previous (myelosuppressive) therapy and bone marrow disease.

#### F. Radiopharmaceutical

1. *Approved name:*  $^{89}\text{Sr}$  – strontium-chloride

*Labeling:* The radiopharmaceutical is supplied in aqueous solution.

*Radiation Dosimetry (ICRP 53):*

<b>Organ</b>	<b>mGy/MBq</b>	<b>rad/mCi</b>
Bone surface	17	63
Red Bone Marrow	11.0	41
Lower Bowel Wall	4.7	17
Bladder Wall	1.3	4.8
Testes	0.80	3.0
Ovaries	0.80	3.0
Uterine Wall	0.80	3.0
Kidneys	0.80	3.0

2. *Approved name:*  $^{153}\text{Sm}$ -samarium-lexidronam [EDTMP]

*Labelling:* The radiopharmaceutical is supplied in aqueous solution.

*Radiation Dosimetry (ICRP 53):*

<b>Organ</b>	<b>mGy/MBq</b>	<b>rad/mCi</b>
Bone surface	6.8	25
Red Bone Marrow	1.5	5.6
Lower Bowel Wall	0.010	0.037
Bladder Wall	1.0	3.7
Testes	0.0050	0.019
Ovaries	0.0090	0.033
Kidneys	0.020	0.074

3. *Approved name:*  $^{186}\text{Re}$ -rhenium-etidronate [HEDP]

*Labelling:* The radiopharmaceutical is supplied in aqueous solution.

*Radiation Dosimetry (ICRP 53):*

<b>Organ</b>	<b>mGy/MBq</b>	<b>rad/mCi</b>
Bone surface	1.4	5.19
Red Bone Marrow	1.3	4.95
Lower Bowel Wall	0.57	2.12
Bladder	0.54	1.98
Testes	0.8	3

Ovaries	0.019	0.07
Kidneys	0.16	0.59

*Quality control:*

The amount of activity to be administered should be checked using an isotope calibrator.

Either of the following two methods can be used to measure the amount of <sup>89</sup>Sr to be administered:

1. Follow the “Guidelines for the Calibration of Metastron (Strontium-89-chloride injection),” available from Amersham Corporation (800/554-0157); or
2. Use a dose calibrator specially configured to quantify beta emissions.

**V. Issues requiring further clarification**

1. Beneficial effect of combined treatment, such as chemotherapy with bone-seeking radiopharmaceuticals, on the survival of patients.
2. Beneficial effects of bone-seeking radiopharmaceuticals in patients receiving bisphosphonates concomitantly.

**VI. Concise bibliography**

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## VII. DISCLAIMER

The European Association of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high quality nuclear medicine therapeutic procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

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