1. Introduction
Osteoblastic skeletal metastases are very common in patients with breast or prostate carcinoma and pain is the most common symptom of skeletal metastases. This pain can be alleviated using analgesics, anaesthetics (usually opiates, which can cause side effects) or external radiation therapy (local or hemi/total body). Systemically administered bone-seeking radiopharmaceuticals can be used as an alternative, one of which is $^{153}$Sm EDTMP (Quadramet®). $^{153}$Sm emits both beta and gamma rays ($E_{\beta_{\text{max}}}=0.81 \text{ MeV}$ and $E_\gamma=103 \text{ keV (29%)}$). The average soft tissue range of $^{153}$Sm is 0.6 mm. The beta particles provide the therapeutic effect whilst the gamma radiation allows post-therapy scintigraphy to be carried out. The physical half-life of $^{153}$Sm is 46.3 h. $^{153}$Sm binds to the bisphosphonate EDTMP which has a high affinity for hydroxyapatite in bone in-vivo. Due to its relatively short half-life, a relatively large amount of radiopharmaceutical is required, and the dose rate is therefore also higher than when using radiopharmaceuticals with a longer half-life. The analgesic effect is fairly fast (<1 week) and can therefore be used successfully for patients who are in a lot of pain and for whom a quick a response is therefore required. The treatment can also be used in patients who have undergone prior chemotherapy since the toxicity level is limited. Treatments can be repeated as necessary provided there are no haematological contraindications (a minimum interval of 8 weeks is recommended). Studies show that 80% of patients treated with $^{153}$Sm-EDTMP experience a reduction in pain.

2. Methodology
This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMMI if available and applicable to the Dutch situation.

3. Indications and contraindications
Patients eligible for treatment should meet the following conditions (at least a and b):

a. Skeletal scintigraphy which shows uptake of bisphosphonate in multiple skeletal metastases from a carcinoma.

b. Pain in several areas despite adequate pain management.

c. Recurring pain in an area previously treated with radiotherapy.

Contraindications

Absolute contraindications:
1. Thrombocyte levels <100x10^9/l
2. Leucocyte levels <3.0x10^9/l
3. Pregnancy
4. Pain in conjunction with a neurological deficit due to metastatic invasion (local treatment is then preferable).
5. Chemotherapy or hemi-body irradiation in the six weeks prior to treatment.
Relative contraindications:
1. Transient, treatable urinary incontinence. (Urinary catheters provided for this purpose should remain in situ for one day)
2. Serum creatinine >130 µmol/l (creatinine clearance <50 ml/min)
3. Preferably, patients should not have undergone chemotherapy or extensive radiotherapy in the previous six months (because of bone marrow reserve)

4. Relation to other therapies
The current standard treatment for painful bone metastases is local external radiation. For recurrent pain in an area which has been irradiated previously, repeat external irradiation is often contraindicated due to myelotoxicity. This disadvantage can be prevented by using therapeutic bone-seeking radiopharmaceuticals at an earlier stage. The effectiveness of these pharmaceuticals is comparable to that of external radiotherapy, involves relatively mild toxicity and is relatively patient-friendly. No comparative studies have yet been carried out to compare the effectiveness of $^{153}$Sm-EDTMP with that of other radiopharmaceuticals such as $^{188}$Re-HEDP and $^{89}$Sr-chloride. External radiotherapy (or even neurosurgery) is always preferable in patients with myelocompression or threatened/current neurological deficit.

Extensive neurological examination should be a standard part of the analysis of patients with painful skeletal metastases. Previous external radiotherapy confined to a limited area is not a contraindication for treatment using $^{153}$Sm-EDTMP. Like $^{188}$Re-HEDP, $^{153}$Sm has the advantage of a short physical half-life accounting for high dose rates and predictable toxicity.

5. Radiopharmaceutical
$^{153}$Sm-EDTMP (EthyleneDiamineTetraMethylenePhosphonate) (Quadramet®)

a. Kinetics
Following intravenous administration, $^{153}$Sm-EDTMP is quickly taken up by bone, and preferentially by bone metastases with an average metastasis-to-normal bone ratio of 5:1. $^{153}$Sm-EDTMP is excreted by the kidneys. Excretion in the urine occurs primarily during the first 4 h (30,3+/−13,5%); 35,3+/−13,6% of the administered activity is excreted in the urine after 12 h. The percentage depends on the degree of skeletal metastasis; the greater the number of metastases, the less $^{153}$Sm-EDTMP is excreted. Likewise, the amount of $^{153}$Sm-EDTMP taken up in the skeleton depends on the degree of metastasis. This is a highly relevant factor in predicting toxicity, which is directly related to the amount of $^{153}$Sm-EDTMP taken up by the skeleton.

b. Dosage
A standard dose of 37 MBq/kg is given (intravenously as a bolus through a free running drip).

6. Radiation safety
Dosimetry
The effective dose of this radiopharmaceutical following injection of 2600 MBq is 796 mSv. The typical radiation dose to the target organ (in this case the skeletal metastases) is 86,5 Gy for an injected activity of 2590 MBq. Typical radiation doses for the following sensitive organs are: normal bone surface area 17,5 Gy, red bone marrow 4,0 Gy, urinary bladder wall 2,5 Gy, kidneys 0,047 Gy and ovaries 0,021 Gy. The absorbed dose in the bone marrow is approximately 1,5 mGy/MBq.
Toxicity/side effects
The toxicity is limited mainly to reversible bone marrow depression which manifests as a temporary drop in thrombocyte and leucocyte levels and which reaches the lowest point in the fourth week following therapy. Recovery often occurs within 6-8 weeks. A temporary ‘flare response’ (increase in pain) can sometimes occur (in approx. 10% of cases). This usually lasts 24-72 h and is often followed by a good response.

7. Patient preparation/essentials for procedure
- Laboratory facilities required.
- Preparatory work must be carried out in a radiopharmacy department compliant with GMP-z.
- Patient preparation, method and after care

Data on request form
a. Type of carcinoma, location of primary tumour and locations of known metastases.
b. Medical history including details of hormonal therapy, chemotherapy and radiotherapy treatments.
c. Result of recent scintigraphy (2-8 weeks) and a copy of the scintigraphy if performed elsewhere.
d. Blood results, in particular any recent thrombocyte and leukocyte counts, serum creatinine levels and creatinine clearance results.
e. Pain medication.

Method
The patient should be well-hydrated beforehand. ¹⁵³Sm-EDTMP is administered as a bolus through a free running drip and using a syringe protected with a lead shield. The radiopharmaceutical is excreted mainly into the urine and the toilet to be used should therefore be connected to sewage, and not to septic tanks. Special sewage tanks are not required (see Aanbevelingen VROM (recommendations of the Dutch Ministry of Housing, Spatial Planning and Environment)). Haematological values should be checked every two weeks following therapy to check whether the thrombocyte levels have returned to normal (after approximately 8 weeks). The first outpatient follow-up appointment should be scheduled for three weeks after treatment and should also include a blood test to check the thrombocyte level. The patient should be seen again one week later if the thrombocyte level is significantly low (maximum drop in thrombocyte count). The following appointment may be scheduled for four weeks later. Follow-up nuclear medicine appointments should be scheduled in close collaboration with the patient’s lead specialist. There is no longer a preference for burial or cremation of patients who die shortly following treatment. Cremation is not considered to pose an unacceptable radiation hazard (crematorium staff can be exposed to doses of up to approximately 1 µSv). Contraception should be used for 4 months following treatment. The product can be administered on an out-patient basis, and there are no restrictions on normal interactions with friends or relations. Incontinent patients should be given sufficient incontinence materials to last five days.
8. Literature