# $^{188}$Re etidronate

$^{188}$Re-HEDP

**1. Indications**

(Multiple) painful osteoblastic bone metastases resulting from solid tumours, with positive $^{99m}$Tc-bisphosphonate skeletal scintigram.
*See Re-188-HEDP Therapy for Skeletal Metastases*

**2. Preparation**

It is important to realize that both the $^{188}$W/$^{188}$Re-generator and the required kit/chemicals are not available as licensed products.
Multiple formulations and methods for the preparation of $^{188}$Re-HEDP have been published. The most extensive work on the preparation of GMP-grade $^{188}$Re-HEDP has recently been published by Lange and ter Heine. Therefore, their composition and preparation method is presented in this recommendation.
Six millilitres of $^{188}$Re-perrhenate (eluate from the $^{188}$W/$^{188}$Re-generator, through a 0,2 µm membrane filter) is mixed with a liquid kit of 2 ml (containing sodium etidronate (50 mg), stannous chloride dihydrate (18,4 mg), gentisic acid (15 mg), hydrochloric acid (to pH ≈ 1,0) and water for injections), after adding 0,2 ml of a solution of 13,4 mg/ml ammonium perrhenate (carrier rhenium). The mixture is heated for 30 min at 90˚C. After cooling, the pH is corrected to 4-6 with 0,5 ml of a 1,5 M solution of sodium acetate. The product is then filtered through a 0,2 µm membrane filter. After carrying out the quality control, the required dose is dispensed in a syringe. The maximum number of patient doses that can be dispensed from one product vial depends on the activity concentration of the eluate.
The addition of carrier (cold) rhenium is indispensable to ensure adequate complexation and in vivo bone accumulation. The access of oxygen must be prohibited to prevent incomplete complexation or re-oxidation of the labelled rhenium to perrhenate.

**3. Quality control**

Visual control: the labelled product is a clear yellow to light brown solution.
pH of the end product, determined with a pH indicator strip: 4-6, using the composition and preparation method described here.
Radiochemical purity, determined with thin layer chromatography analogous to technetium-bisphosphonate complexes. Paper chromatography can be applied, using Whatman 3 MM cellulose strips. Two systems are used to separate the different radiochemical species. For determination of free perrhenate ($^{188}ReO_4^-$), the mobile phase is acetone. In this system the $^{188}$Re-HEDP complex and reduced (colloidal) rhenium ($^{188}ReO_2$) remain at the application spot and $^{188}ReO_4^-$ migrates with the mobile phase. For determination of $^{188}ReO_2$ a 0,01 M disodium etidronate solution in sodium chloride 0,9% is used. In this system, $^{188}ReO_2$ remains at the application spot and the $^{188}$Re-HEDP complex and $^{188}ReO_{4-}$ migrate with the mobile phase. The radiochemical purity can then be calculated as follows: 100 - [amount of free $ReO_4^-$ (%) + amount of free $ReO_2$ (%)].

The specification for radiochemical purity of the drug product is >93%, defined as the relative $^{188}$Re content in the radiochemical form of $^{188}$Re-HEDP.

**4. Stability**

Using the composition and preparation method described here, the stability is 24 h at room temperature, both in a vial and in a syringe.

**5. Biodistribution & pharmacokinetics**

After intravenous injection, $^{188}$Re-HEDP shows a fast uptake in the skeleton, where it is mainly accumulated in regions with a fast bone turnover, such as osteoblastic bone metastases, where it binds to hydroxyapatite. The mean effective half-life in bone metastases is 16h. Unbound $^{188}$Re-HEDP is rapidly excreted via the kidneys.

**6. Adverse reactions**

After injection of a therapeutic dose a temporary bone marrow depression can occur, with a nadir in thrombocyte and leukocyte counts is seen about 4 weeks after injection. This haematological toxicity is mostly grade I or II and needs no intervention.
Next to the haematological adverse effects, a flare reaction (a temporary worsening of the pain) may be experienced 1-3 days after injection.

**7. Interactions and contra-indications**

Interactions: unknown. Therapy with $^{188}$Re-HEDP can be combined with oral bisphosphonates.
Contra-indications: thrombocytes <100x10$^9$/l, leukocytes <3,0x10$^9$/l, acute neurological symptoms requiring urgent external beam radiation, pregnancy, breast-feeding.
*See Re-188-HEDP Therapy for Skeletal Metastases*

**8. Literature**


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