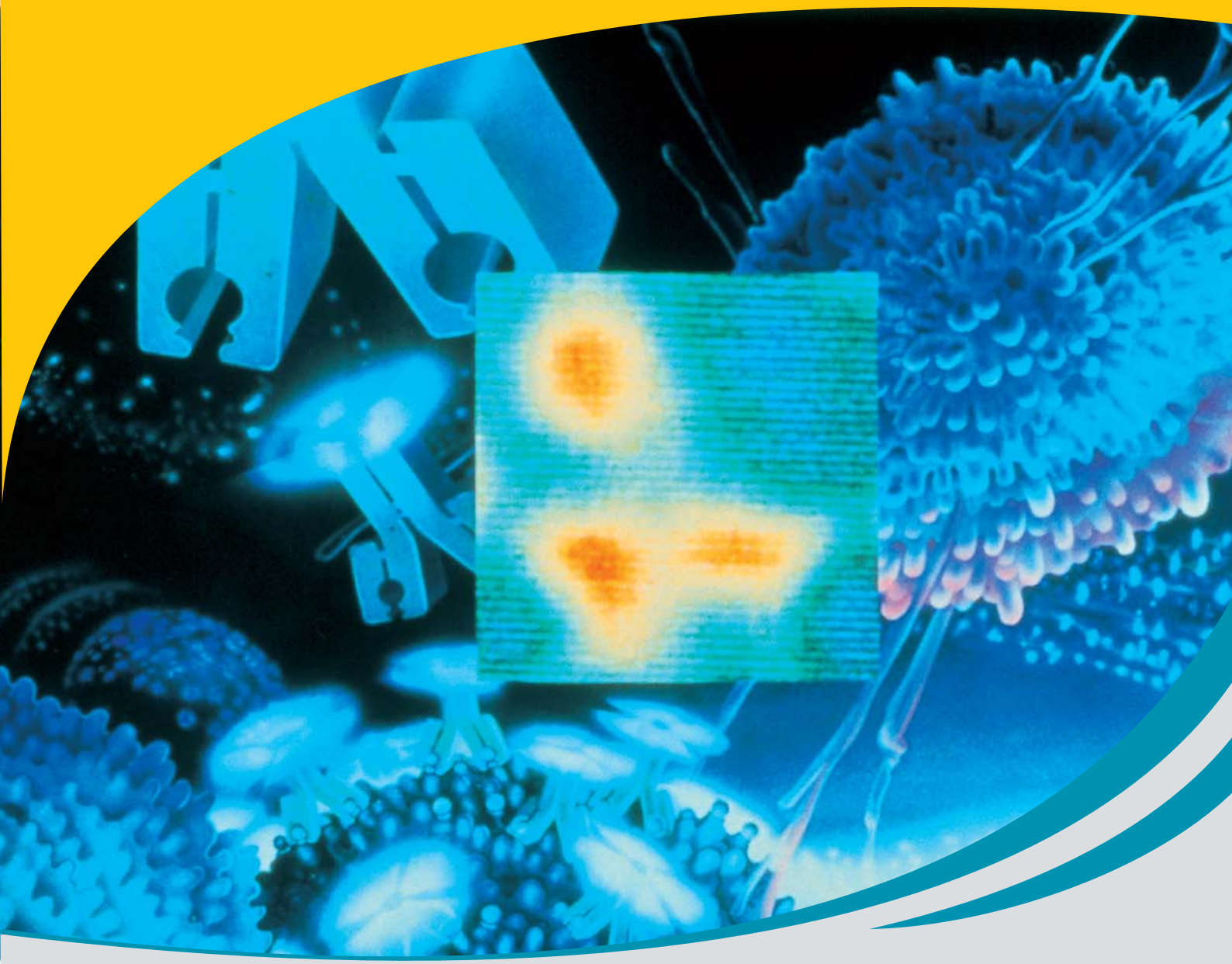
KIT FOR LABELLING



# SCINTIMUN®
# Granulocyte

Monoclonal Antibody (MAb) BW 250/183
with Technetium-99m for intravenous injection

## An imaging tool for:

- Detection of inflammatory processes
- Detection of bone marrow metastases

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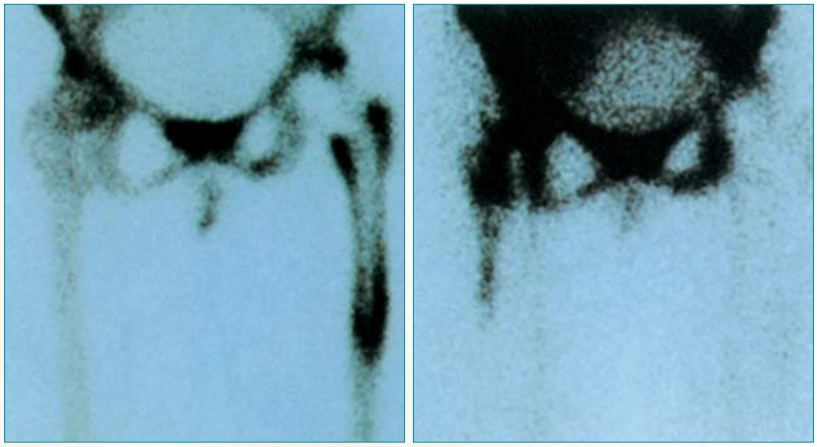
# The radiopharmaceutical of choice for inflammation and bone marrow imaging

*ANTERIOR VIEW*



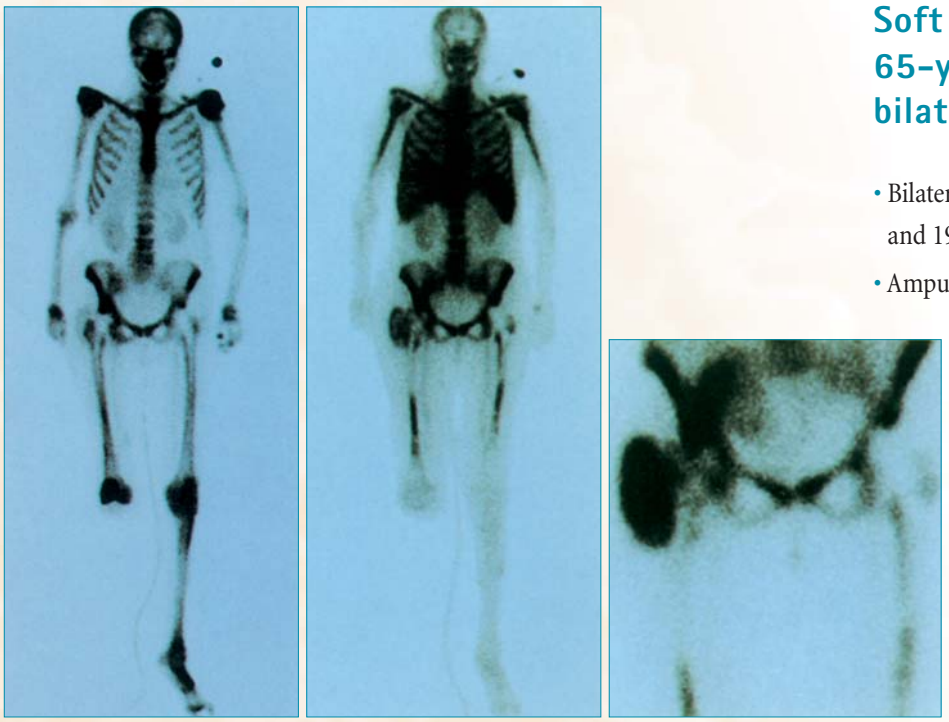
$^{99m}$Tc-MDP

$^{99m}$Tc-anti-Granulocyte BW 250/183
24h p.i.

## Loosening of hip prosthesis in a 46-yr-old woman suffering from pain.

- Left hip total prosthesis implant in August 1997.
- Exploration for pain and source of infection.
- $^{99m}$Tc-MDP scintigraphy clearly shows bone changes which cause loosening around shaft of left prosthesis.
- **$^{99m}$Tc-anti-Granulocyte BW 250/183** scintigraphy is normal.
- Final diagnosis, after surgery, shows an aseptic loosening of this left hip prosthesis.

*ANTERIOR VIEWS*



$^{99m}$Tc-MDP

$^{99m}$Tc-anti-Granulocyte BW 250/183
6h p.i. 24h p.i.

## Soft tissue inflammation in a 65-yr-old woman with bilateral prosthesis.

- Bilateral hip total prosthesis implant in 1985 and 1988.
- Amputation of right lower leg due to chronic ischemia of the lower extremities.
- Suspected infection in region of right hip.
- $^{99m}$Tc-MDP scintigraphy shows no evidence of infection of right hip joint.
- **$^{99m}$Tc-anti-Granulocyte BW 250/183** scintigraphy shows :
- Large abscess lateral to right hip joint.
- Left hip prosthesis in normal position, with no sign of irritation or infection.
- No infection in right stump.

**Due to the high specificity of the in vivo cell labelling, Scintimun® Granulocyte offers a simpler, faster and non destructive method for inflammation detection and bone marrow imaging.**

# Summary of Product Characteristics

## 1. NAME OF MEDICINAL PRODUCT

**Scintimun® Granulocyte**

Kit for labelling the monoclonal antibody (MAb) BW 250/183 with technetium-99m for intravenous injection.
The Scintimun® Granulocyte kit is a radiopharmaceutical product for diagnostic use.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The Scintimun® Granulocyte kit contains two sets of vials 1 and vials 2. The technetium-99m radioisotope is not included in the kit.
Each vial 1 of 5 mg dry substance contains 1 mg of anti-granulocyte BW 250/183 murine IgG1 antibody. After reconstitution, the vial 1 contains 1 mg/ml of antibody.
For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Powder for injection.

## 4. CLINICAL PARTICULARS

### 4.1. Diagnostic indications

This medicinal product is for diagnostic use only.
After reconstitution with sodium pertechnetate [$^{99m}$Tc] injection, the product is used for :
- Immunoscintigraphy of inflammations.
- Bone marrow scintigraphy, particularly where there is a suspicion of metastases in the medullar space.

### 4.2. Posology and method of administration

The single injection of [$^{99m}$Tc]-labelled antibody must be given strictly intravenously and in the complete dose.
The doses used are between 200 and 800 MBq of [$^{99m}$Tc]-labelled antibody :
- 200-400 MBq (5-11 mCi) for bone marrow scintigraphy
- 400-800 MBq (11-22 mCi) for the detection of inflammation.

The amount of protein used can vary between 0.25 and 1.0 mg (1/4 to 1 labelling unit).
The immunoscintigraphy can begin 3 to 6 h after administration.
Late imaging, e.g. 24 h after the injection, may be useful in pinpointing inflammation, depending on the objective.
This can be carried out in two-dimensional presentations or in the SPECT mode. More activity is required for the evaluation of SPECT images than for two-dimensional images taken with a conventional scintillation camera.

### 4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.
The indication must be particularly strictly established in young people and in breastfeeding mothers.
In the absence of a vital indication, Scintimun® Granulocyte should not be used during pregnancy.

### 4.4. Special warning and precautions for use

This radiopharmaceutical may be used and administered only by authorised persons.
Radioactive products must be handled with particular care to keep radiation loading for both the patient and staff to a minimum.
Radiopharmaceuticals intended for administration to patients should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical quality requirements.
Liquid radioactive waste, contaminated drug vials, syringes and cannulas must be treated as stated in relevant articles of the current Radiation Protection Decree.

### 4.5. Interaction with other medicinal products and other forms of interaction

There are no known interactions with other drugs.
An interval of at least 2 days must be allowed after any previous investigation with other 99mTc-labelled drugs.

### 4.6. Pregnancy and lactation

The indication must be particularly strictly established in breastfeeding mothers.
In the absence of a vital indication, Scintimun® Granulocyte should not be used during pregnancy.

### 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. Anyway, this kind of secondary effect was not noted in the clinical studies.

### 4.8. Undesirable effects

Administration of monoclonal murine antibodies can lead to the development of anti-mouse immunoglobulin antibodies (HAMA), which may impair the sensitivity of the lesion imaging.
For this reason, and especially for reasons of patient safety, a HAMA test must be carried out with the patient's serum before each repeated administration of monoclonal murine antibodies.
The antibody used here has a particularly weak immunogenic action in the stated dose range. Fewer than 5 % of the patients developed HAMAs after a single administration.
Since allergic reactions to the murine protein cannot be ruled out, cardiovascular drugs, corticosteroids, and anti-histamines must be kept at hand during each administration of the product. This is particularly important if a test for anti-mouse immunoglobulin antibodies (HAMA test) has not been first carried out on the patient's serum.

### 4.9. Overdose

In the event of the administration of an overdose of a radiopharmaceutical, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body.
In the event of an overdose of this technetium [$^{99m}$Tc] labelled compound, laxatives to aid faecal clearance are recommended.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

$^{99m}$Tc-labelled monoclonal CEA-NCA specific antibody BW 250/183 is a diagnostic aid reacting with more than 90 % of granulocytes in peripheral blood and with granulocytes and in some cases also myelocytes in bone marrow. After labelling with $^{99m}$Tc-pertechnetate, the monoclonal antibody is suitable for in-vivo labelling of granulocytes and thus for scintigraphic imaging of granulocyte accumulations (i.e. inflammations) and for bone marrow scintigraphy. Since the antibody does not impair granulocyte function, the investigation has no effect on the blood granulocyte count.

### 5.2. Pharmacokinetic properties

In the first 24 h less than 5 % of the radioactivity is excreted. This comparatively small amount is sufficient to image the kidneys and bladder. The elimination of labelled cells from blood normally occurs with the biological half-life of the granulocytes, equal to about 6 h.
Apart from the intravascular labelling of circulating granulocytes, another effect is extravasation of the antibody and its binding to cells in the periphery. Since some granulocyte precursors also show the corresponding antigen, bone marrow is the most important target tissue.
Initially about one third of the antibodies are quickly bound specifically in the bone marrow. Since the spleen acts as a pool organ for granulocytes a clear accumulation of radioactivity occurs there as well. About 2-5 % of the injected activity is found in the spleen ; the scatter can be particularly wide here depending on the state of health of the patient. In addition to this, radioactivity accumulates in the liver, the pool values rising from an initial 15 % of the injected activity to more than 30 % in some cases. In the patient's blood about 1/4 of the antibodies are present in cell-bound form after the first hour. The remaining antibodies circulate freely, can also leave the vascular space, and are available for direct binding to cells at the periphery.
In the event of immunisation with murine IgG the formation of immunocomplexes may lead to a sharp reduction in the serum half-life and in extreme cases liver storage may consequently increase to still greater values.

### 5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of acute toxicity and genotoxicity.
Preclinical effects were observed (on the spleen weight) in repeated dose toxicity studies only at exposures considered sufficiently in excess of the maximum human exposure (70 times the human therapeutic dose) indicating little relevance to clinical use.
No animal studies regarding carcinogenic potential and toxicity to reproduction were performed. This agent is not intended for regular or continuous administration.
However, potentially toxic effects produced directly by specificity of the antibody cannot be investigated experimentally. Since binding of the antibody to foetal tissue cannot be ruled out, pregnancy is a contra-indication.

### 5.4. Radiation dosimetry

Radiation loading was calculated using the MIRD concept. Where available, data on distribution in man were used ; the remaining data have been determined from distribution studies in rats. The calculation of the effective dose is based exclusively on human data.

| | | |
|---|---|---|
| **Liver** | 0.022 mGy/MBq | (81 mrad/mCi) |
| **Lung** | 0.008 mGy/MBq | (30 mrad/mCi) |
| **Spleen** | 0.029 mGy/MBq | (107 mrad/mCi) |
| **Kidneys** | 0.019 mGy/MBq | (70 mrad/mCi) |
| **Bone marrow** | 0.029 mGy/MBq | (109 mrad/mCi) |
| **Gonads** | 0.006 mGy/MBq | (22 mrad/mCi) |
| **Rest of body** | 0.005 mGy/MBq | (19 mrad/mCi) |
| **Effective dose** | 0.011 mSv/MBq | (42 mrem/mCi). |

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

**The composition of each vial is as follow :**

Each vial 1 contains, in addition of 1 mg of antibody BW 250/183 (active substance) :

2 mg sodium phosphate
2 mg D-glucitol (sorbitol)

Each vial 2 contains :

2.7 mg tetrasodium 1, 1, 3, 3-propane-tetraphosphonate dihydrate (PTP)
0.12 mg tin(II) chloride dihydrate
0.2 mg sodium chloride

The product contains no anti-microbial preservatives.

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf life

Stability of the original pack is guaranteed until the expiry date given on the packaging and bottle label. The kit must not be used after the expiry date.

### 6.4. Special precautions for storage

Store at 2-8°C in the original package and protected from light.
The storage stability of the labelled injection solution in the original sealed glass bottles protected from atmospheric oxygen and light is limited to 3 h.

### 6.5. Nature and contents of container

Colourless, type I glass vials, closed with chlorobutyl rubber stoppers and aluminium crimped capsules.

### 6.6. Instructions for use and handling

1. Dissolve the dry substance from bottle 2 (the tin(II)-PTP component) in 5 ml of additive-free 0.9% sodium chloride solution.
2. When contents of bottle 2 have completely dissolved, transfer 1 ml of this solution with a syringe into bottle 1 (the antibody component) of the kit. The contents of bottle 1 will dissolve within one minute (do not invert or shake).
3. After 1 min check to see whether the contents of bottle 1 have dissolved completely. Then place bottle 1 behind suitable screening and treat with 2-7 ml of $^{99m}$Tc-pertechnetate (in accordance with current Eur. Ph.). The entire solution must not be inverted or shaken.
4. Fill in the enclosed label and affix it to the preparation.
5. 10 min after the addition of radioactivity the injection solution is ready for use.

**Notes on the instructions**

- Bottles 1 and 2 may only be used together if their Batch numbers are those given on the packaging in which they are both wrapped.
- Under no circumstances may the tin(II)-PTP component (bottle 2) be labelled first and then added to the antibody (bottle 1).
- The prepared injection solution must be protected from oxygen.

**Specification of the injection solution**

1 mg MAb BW 250/183 (murine)
0.5 mg tetrasodium 1,1,3,3-propane- tetraphosphonate - 2H2O (PTP)
2 mg sodium phosphate
0.2 mg tin(II) chloride
2 mg D-glucitol (sorbitol)
300-1800 MBq(8.1- 48.6 mCi) technetium-99m
3-8 ml water
pH 6.5 - 7.5

The clear solution is isotonic and sterile and pyrogen-free as long as aseptic working conditions have been observed. The solution also contains varying quantities of sodium chloride, depending on the volume of eluate (2-7 ml). The specification of the injection solution depends on the generator eluate used and must therefore be supplemented accordingly.

**Quality control**

The quality of labelling (radiochemical purity) may be checked according to the following procedure.

**Method**

Instant Thin Layer Chromatography.

**Materials and reagents**

*1. Adsorbent :*
ITLC plates (Gelman SG). Trace a starting line 2.5 cm from the bottom of the paper strip.

*2. Solvent :*
Methanol:water: 8:2 (V/V).

*3. Containers :*
Appropriate containers such as chromatography tank, Erlenmeyer flasks.

*4. Miscellaneous :*
Forceps, scissors, syringes, appropriate counting assembly.

**Procedure**

Do not let air enter the vial to be tested and store all vials containing radioactive solution in lead shieldings.

1. Apply a spot of the preparation to the starting line of the paper strip using a syringe.
2. Using forceps, introduce the paper strip vertically into the chromatography tank for development with the starting line downward. Stopper the chromatography tank.
3. When the solvent has reached the top of the strip, use the forceps to remove the strip and dry in the air.
4. Cut the strip at Rf = 0.5.
5. Separately count each section of the strip and record the obtained values (use an appropriate detection apparatus with a constant counting time, and known geometry and background noise).
6. Calculations
   Correct the counting data for background noise.
   Calculate the percentage of free technetium [$^{99m}$Tc] :

$$\% \text{ free } {}^{99m}\text{Tc} = \frac{\text{Activity of strip for Rf0.5-1.0}}{\text{Total activity of strip}} \times 100$$

Calculate the percentage of bound technetium [$^{99m}$Tc] (radiochemical purity) :
% bound $^{99m}$Tc = 100 % - % free $^{99m}$Tc
7. The percentage of bound $^{99m}$Tc (radiochemical purity) should be more than 95%.

The administration of radiopharmaceuticals creates risks for 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.
Radioactive waste must be disposed of in conformity with the relevant national and international regulations.
Any unused product or waste material should be disposed of in accordance with local requirements.

## 7. ADDITIONAL INFORMATION

Please note ! For current prescribing information, refer to package insert and/or contact your local CISBIO International organisation.

## 8. DATE OF (PARTIAL) REVISION OF THE TEXT

13/05/2002

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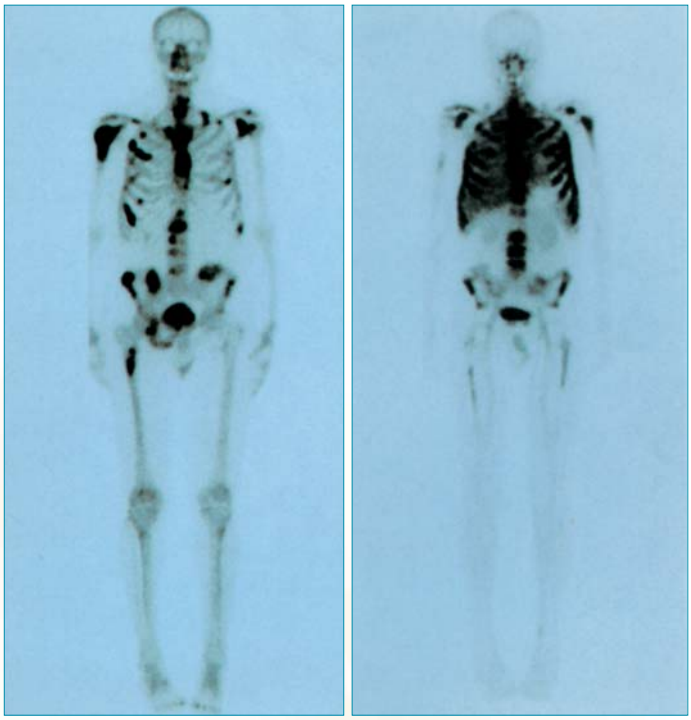
*ANTERIOR VIEWS*



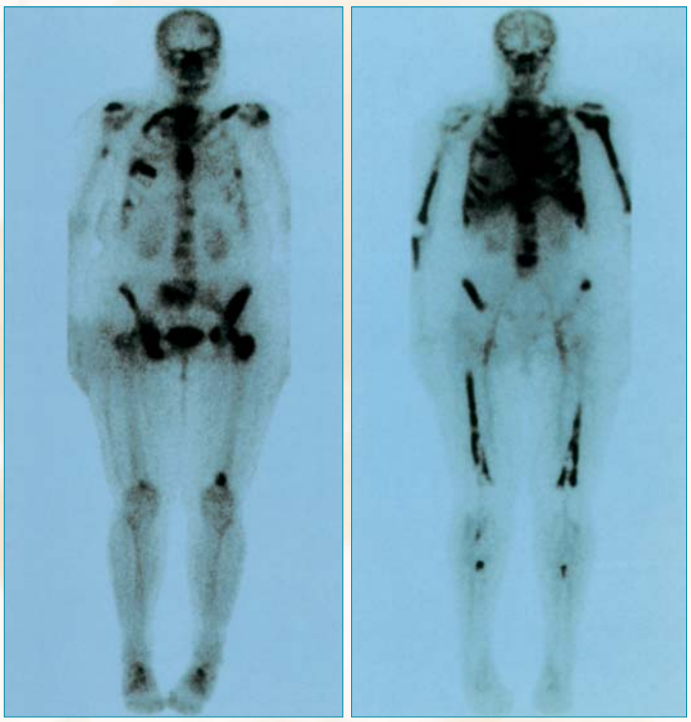
$^{99m}$Tc-MDP

$^{99m}$Tc-anti-Granulocyte BW 250/183
**5h p.i.**

## Multiple bone metastases in a 65-yr-old man suffering from prostatic carcinoma.

- Increasing bone pain.
- $^{99m}$Tc-MDP scintigraphy shows lesions in the skeleton.
- **$^{99m}$Tc-anti-Granulocyte BW 250/183** scintigraphy shows the same lesions in the skeleton. Some additional pathological foci in the ribs are discovered.

*ANTERIOR VIEWS*



$^{99m}$Tc-MDP

$^{99m}$Tc-anti-Granulocyte BW 250/183
**4h p.i.**

## Multiple bone metastases in a 45yr-old woman suffering from breast cancer.

- $^{99m}$Tc-MDP scintigraphy shows metastatic lesions.
- **$^{99m}$Tc-anti-Granulocyte BW 250/183** scintigraphy shows corresponding lesions and in addition, more hot lesions especially in the right humerus, ribs, pelvis and the peripheral marrow extension.

**With the courtesy of Pr. Dr. J. Locher, and Dr. K. Seybold, Cantonal Hospital Aarau, Switzerland.**

# SCINTIMUN® Granulocyte

## A Diagnostic Kit for Technetium-99m Labelling of Monoclonal Antibody BW 250/183

| | |
|---|---|
| • High specificity for human granulocyte | NCA-95 antigen. |
| • A high in vivo granulocyte selectivity | > 90% binding to granulocytes. |
| • High affinity constant for NCA-95 antigen | 2 x 109 l/mol. |
| • A rapid blood clearance | 55% to 60% of the I.D. in the first 4 hours p.i. |
| • Early binding to circulating granulocytes | > 10% - 20% of I.D. in the first 4 hours p.i. |
| • Stable in vivo labelling | > 24 hours. |
| • High uptake to precursor cells of granulocytes giving high bone marrow uptake | 40% to 50% of I.D., 4 hours after injection. |
| • Optimal imaging | Both planar and SPECT scans may be carried out.<br>- The first acquisition should be done 3-6 hours after administration.<br>- Late imaging e.g. 24 h after injection may be performed if necessary. |
| • Labelled with $^{99m}$Tc | A recommended activity of :<br>- 200-400 MBq for bone marrow imaging.<br>- 400-800 MBq for detection of inflammation. |
| • Easy to use | A single intravenous injection of a quantity ranging between 0.25 mg to 1 mg of antibody is required. |
| • Immunological response | < 5% HAMA incidence. |
| • Safe for patients and medical staff | |

NCA-95 : non reacting cross antigen 95, I.D. : injected dose, p.i. : post injection

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