

Making bone inflammation/infection simpler to detect

Scintimun® 1mg

1 High confidence in your diagnostic

Whole IgG1 antibody offering high specificity of inflammation/infection process

➤ Specific binding

to 99.6% of mature human granulocytes⁽¹⁾ with a high specificity for NCA 95 antigen expressed on granulocyte as well as in granulopoietic bone marrow cells⁽²⁾ with no alteration of granulocyte functions⁽³⁾ and no cross-reactivity with human platelets⁽⁴⁾

➤ High affinity binding

2×10^9 L/mol⁽⁵⁾

➤ Efficient accumulation in inflammation/infection site by two main processes

By accumulation of labeled circulating granulocytes (10-20%) and by the labeling of granulocytes already migrated⁽⁶⁾⁽⁷⁾ into inflammation/infection site

➤ Optimal balance between blood clearance and target uptake for an optimal image quality⁽⁸⁾

- Rapid blood clearance (50% of injected activity eliminated in 1 hr, 75% in 5 hr)
- In blood, the injected activity is existing as free radiolabeled antibody (25%) and is bound to circulating granulocytes (10-20%) 4hr after injection
- Rapid and persistent uptake in bone marrow (37%) 4hr after injection
- Low urinary excretion (less than 14% at 24hr)

High target to blood ratio for optimal visualisation of inflammation/infection site

➤ Possibility to repeat images 24hr after injection in order to confort the diagnosis

Scintimun® 1 mg kit for radiopharmaceutical preparation, besilesomab

(Murine monoclonal antibody)

PRESENTATION Kit composed of 1 or 2 multidose vials Scintimun®

Vial Scintimun®

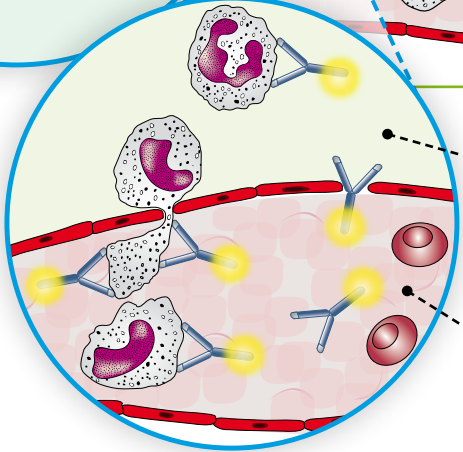
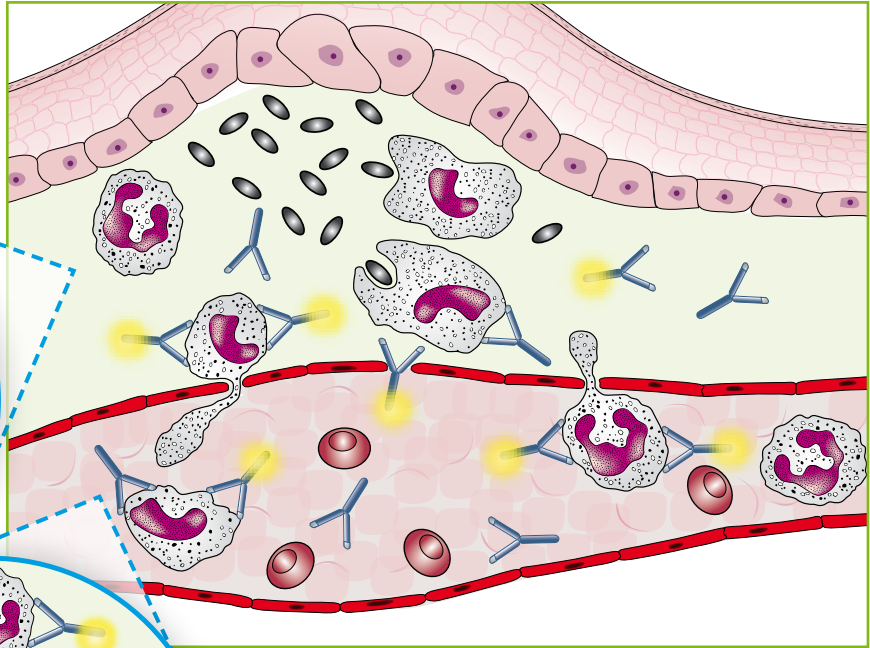
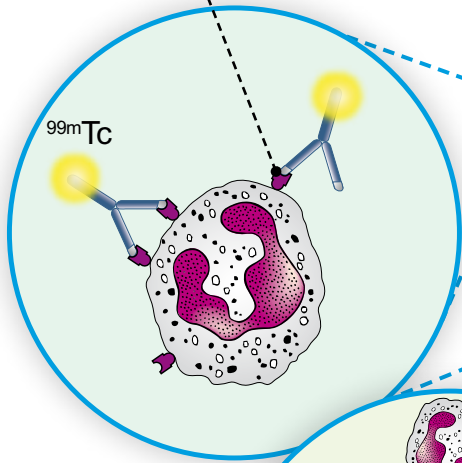
- Besilesomab (1mg)
- Sodium dihydrogen phosphate, anhydrous
- Disodium monohydrogen phosphate, anhydrous
- Sorbitol E420
- Under nitrogen atmosphere

Vial Solvent for Scintimun®

- 1, 1, 3, 3-propane tetraphosphonic acid, tetrasodium salt, dihydrate (PTP)
- Stannous chloride dihydrate
- Sodium hydroxide / Hydrochloric acid (for pH adjustment)
- Nitrogen

NCA-95 antigen
over expressed
in activated granulocyte.

High affinity binding
 $2 \cdot 10^9$ L/mol



Labeling
to already
migrated
granulocyte
(passive)

Direct labeling
in blood stream
(active)

Inflammatory / infection area.
Granulocytes are the first immune
cells to migrate from the circulating
blood stream to
the inflammatory site.

2 High flexibility & productivity

- **Easy and accessible to all nuclear medicine departments**
No dedicated laboratory is required.
Scintimun® is provided under kit formulation

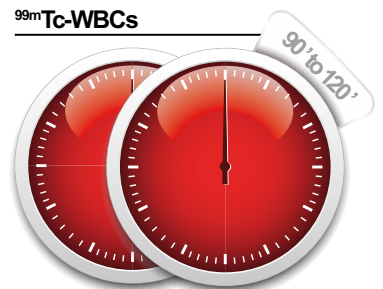
- **Quick preparation**

Scintimun®



One step ready to use

^{99m}Tc -WBCs



Multisteps process from
patient's white blood cells
(Isolation + in vitro labeling)

3 Safety in preparation and use

➤ **A direct in vivo cell labeling:**

No blood handling

➤ **HAMA⁽⁹⁾ (Human Anti-Mouse Antibody)**

Of the 116 patients who had at least one HAMA assessment after administration of technetium (^{99m}Tc) besilesomab in the phase III study, 16 patients (14%) showed positive HAMA levels without any hypersensitivity events

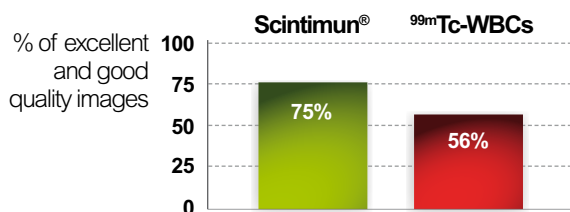
➤ **Experience**

Since its marketing launch more than 15 years ago, around 100 000 patients have been administered technetium (^{99m}Tc)-besilesomab without severe safety concerns. Almost 1 200 patients were studied in various company-sponsored trials. Current administration rate is 8 000 to 10 000 new patients per year

4 Highest standards performance

Main outcome of the phase III study (AG-PH3)⁽⁹⁾

- Good agreement of Scintimun[®] findings with labeled ^{99m}Tc-WBCs
- Higher image quality Scintimun[®] vs ^{99m}Tc-WBCs



Main outcome of the phase III 7MN-301-SZ-A⁽¹⁰⁾

- Additional information for patient management in more than 40% of patients
- Positive impact on therapeutic decisions in 55% of patients

Clinical indication :

- Scintigraphic imaging, in conjunction with other appropriate imaging modalities, for determining the location of inflammation/infection in peripheral bone in adults with suspected osteomyelitis
- Scintimun[®] should not be used for the diagnosis of diabetic foot infection

(1) Hirt. Orpegen Pharma report 9-14-02. Flow cytometric analysis of human bone marrow CD34+ cells labelled with MAb BW 250/183. February 13, 2008.

(2) Bosslet "Binding to blood cells", Study MAb BW 250/183-BS-9 Sep6, 1988

(3) Bosslet "Influence of MAb BW 250/183 on granulocyte functions" BS612 Sept 6 1988

(4) Mimouni "Cross reactivity of besilesomab with human platelets and granulocytes from doses" – Report 348 44EP

(5) Steinsträsser A et al. Binding of the monoclonal antibody BW 250/183 to human granulocytes. Nucl Med 1992; 31: 57-63.

(6) Clinical trial ref 7 MN-302SZ-A, 7D-101 SZ-A

(7) Becker W, Repp R et al: Eur J Nucl Med 1989; 15: 361-366

(8) Clinical trial ref 7 MN-302SZ-A, 7D-101SZ-A" (decay corrected values)

(9) Clinical trial ref AG-PH3

(10) Clinical trial ref 7 MN-301SZ-A

Summary of Product Characteristics

PRESCRIBING INFORMATION: SCINTIMUN® 1 mg KIT FOR RADIOPHARMACEUTICAL PREPARATION

Please refer to the full Summary of Product Characteristics (SPC) before prescribing. Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.

PRESENTATION

Vial containing 1 mg of besilesomab, anti-granulocyte monoclonal antibody (BW 250/183), produced in murine cells.
Excipients: contains 2 mg of sorbitol / vial of Scintimun®

DIAGNOSTIC INDICATIONS

Scintigraphic imaging, in conjunction with other appropriate imaging modalities, for determining the location of inflammation/infection in peripheral bone in adults with suspected osteomyelitis. Scintimun® should not be used for the diagnosis of diabetic foot infection.

DOSAGE AND METHOD OF ADMINISTRATION

Scintimun® should be reconstituted with the solvent provided and then radiolabelled with sodium pertechnetate (^{99m}Tc) injection in order to obtain a clear and colourless technetium (^{99m}Tc) besilesomab injection.

In adults, the recommended activity of technetium (^{99m}Tc) besilesomab should be between 400 MBq and 800 MBq. This corresponds to the administration of 0.25 to 1 mg of besilesomab. Scintimun® is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy. Scintimun® should be given to sufficiently hydrated patients. In order to obtain images of best quality and to reduce the radiation exposure of the bladder, patients should be encouraged to drink sufficient amounts and to empty their bladder prior to and after the scintigraphic examination. SPECT imaging should start 3 to 6 hours after administration. An additional acquisition 24 hours after initial injection is recommended. Acquisition can be performed using planar imaging.

CONTRAINDICATIONS

In patients with hypersensitivity to besilesomab, other murine antibodies or any of the excipients, in patients with positive screening test for human anti-mouse antibody (HAMA), and pregnancy.

WARNINGS AND PRECAUTIONS

This medicinal product is for use in designated nuclear medicine facilities only, and should only be handled by authorised personnel. It should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements.

There are currently no criteria to distinguish infection and inflammation by means of Scintimun® imaging. Scintimun® images should be interpreted in the context of other appropriate anatomical and/or functional imaging examinations.

Only limited data is available about binding of technetium (^{99m}Tc) besilesomab to CarcinoEmbryonic Antigen (CEA) expressing tumours in vivo. In vitro, besilesomab cross-reacts with CEA. False positive findings in patients with CEA expressing tumours cannot be excluded.

False results may be obtained in patients with diseases involving neutrophil defects and to patients with haematological malignancies including myeloma.

Scintimun® contains sorbitol therefore patients with rare hereditary problems of fructose intolerance should not be administered this product.

Human Anti-Mouse Antibodies (HAMA): Administration of murine monoclonal antibodies can lead to the development of Human

Anti-Mouse Antibodies (HAMA). Patients who are HAMA positive may have a greater risk for hypersensitivity reactions. Inquiry on possible previous exposure to murine monoclonal antibodies and a HAMA test should be made prior to administration of Scintimun®; a positive response would contraindicate the administration of Scintimun®.

Repeated use: Scintimun® should only be used once in a patient's lifetime.

Hypersensitivity reactions: Anaphylactic or anaphylactoid reactions may occur after administration of the medicinal product. Appropriate cardiopulmonary resuscitation facilities and trained personnel should be available for immediate use in the event of an adverse reaction. Since allergic reactions to the murine protein cannot be excluded, cardiovascular treatment, corticosteroids, and antihistamines must be available during administration of the product.

An interval of at least 2 days must be observed between any previous scintigraphy with other technetium (^{99m}Tc)-labelled agents and administration of Scintimun.

INTERACTIONS

Active substances which inhibit inflammation or affect the haematopoietic system (such as antibiotics and corticosteroids) may lead to false negative results. Such substances should therefore not be administered together with, or a short time before the injection of Scintimun®.

PREGNANCY AND LACTATION

Contraindicated in pregnancy. Information should be sought about pregnancy from women of child bearing potential. A woman who has missed her period should be assumed to be pregnant. If administration to a breast feeding woman is necessary, breast-feeding should be interrupted for three days. A close contact with the child should also be avoided during the first 12 hours after the injection.

UNDESIRABLE EFFECTS

Human anti-mouse antibody positive reaction is a very common side effect; hypotension is common. Hypersensitivity, including angioedema, urticaria is uncommon. Rare effects include anaphylactic/anaphylactoid reaction, myalgia and arthralgia. Exposure to ionising radiation is linked with cancer induction and a potential for hereditary defects and must be kept as low as reasonably achievable.

DOSIMETRY

Effective dose from 800 MBq is 6.9 mSv.

OVERDOSE

Encourage frequent micturition and defecation.

MARKETING AUTHORISATION HOLDER

CIS bio international, B.P. 32, F-91192 Gif-sur-Yvette Cedex, France.

CLASSIFICATION FOR SUPPLY

Subject to restricted medical prescription.

MARKETING AUTHORISATION NUMBERS

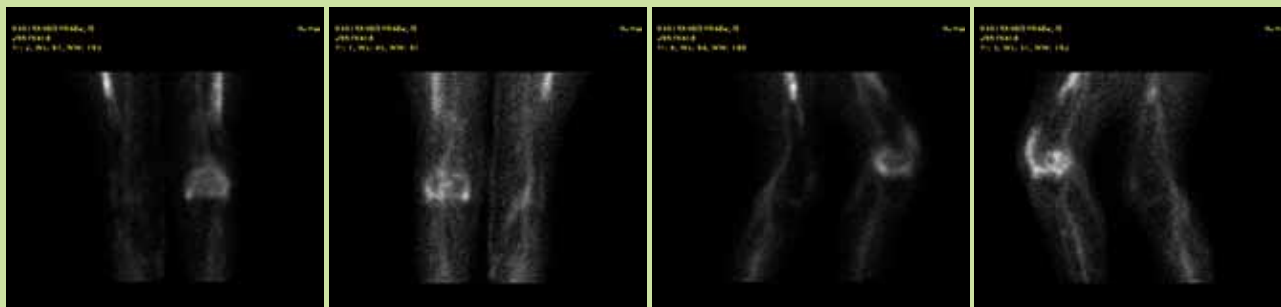
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DATE OF REVISION OF TEXT

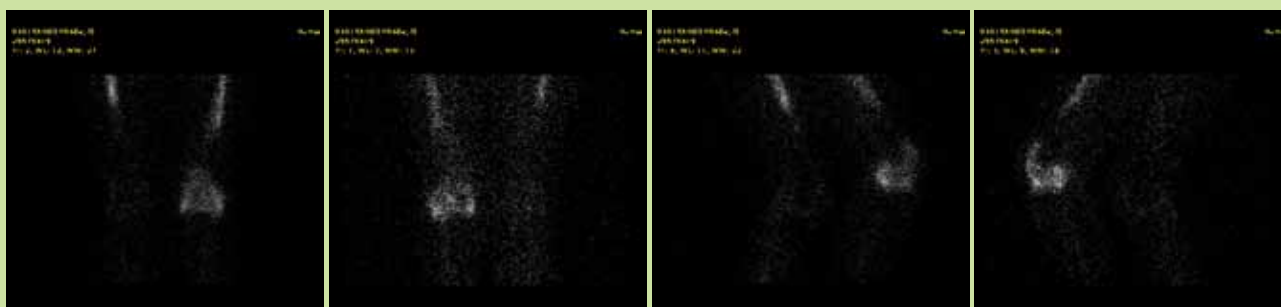
11 January 2010

PLEASE REPORT ANY ADVERSE EVENTS TO HEALTH AUTHORITIES and/or CIS BIO INTERNATIONAL.

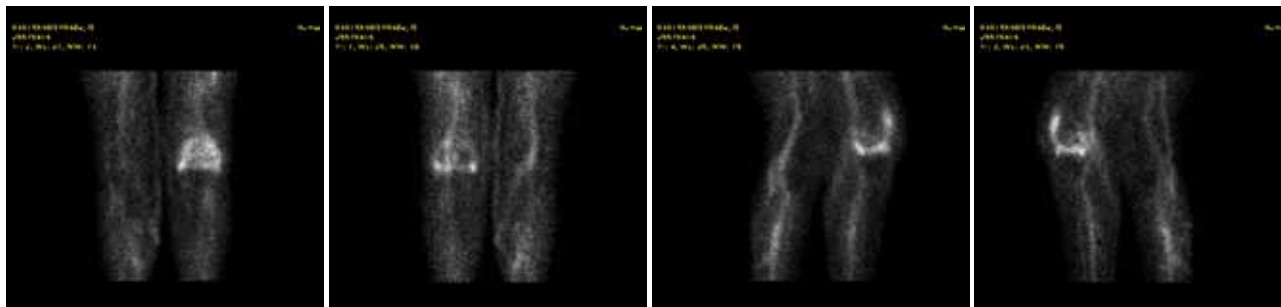
4hr



24hr



4hr



24hr

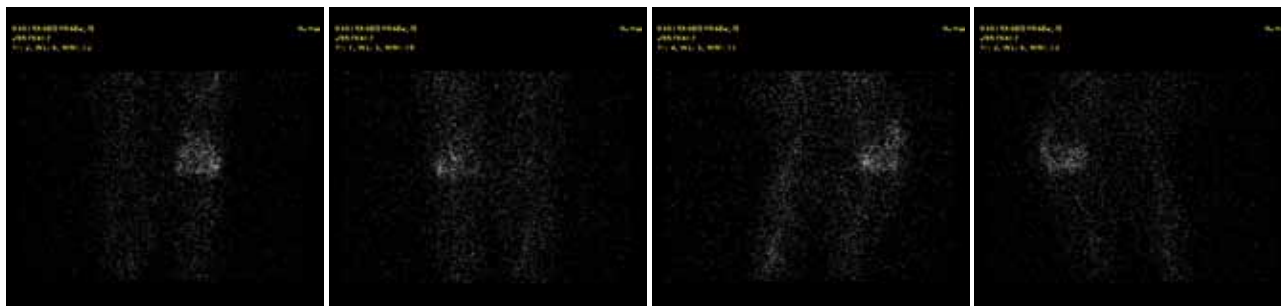


Fig. 1 : Scintimun® and ^{99m}Tc-WBCs scans of the infected total left knee prosthesis

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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.*



Making bone inflammation/ infection simpler to detect

Scintimun[®] 1mg



▲▼ Scintimun® vs ^{99m}Tc-WBCs

A patient, a 66 year old woman, underwent surgery for a total left knee prosthesis in May 2005. Initially she had no complaints, but in 2006 she reported a painful knee at the site of the prosthesis.

In February 2006 she got a revision surgery of the total knee prosthesis.

One year later, at physical examination the left knee was swollen, painful and warm. Infection was suspected.

A bone scan performed in March 2007, also suggested infection.

In May 2007, a puncture in the knee showed no bacteria, but a lot of leucocytes. The patient was imaged by Scintimun® and ^{99m}Tc-WBC scintigraphies at 2 days of interval (Fig.1). Both imaging procedures concluded for infection.

Despite negative bacterial culture, antibiotics were started because of the scintigraphic findings. In the following months, the patient felt better, however some pain remained in the left knee. Expectative care was recommended. Because of the benefit of the antibiotics, the final conclusion was an infection of the knee prosthesis.



New active ingredient according to Spanish Royal Decree 1344/2007



New product under intensive monitoring in United Kingdom