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
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 \(\times 10^{9}\) 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®

<table>
<thead>
<tr>
<th>Vial Scintimun®</th>
<th>Vial Solvent for Scintimun®</th>
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</thead>
<tbody>
<tr>
<td>• Besilesomab (1mg)</td>
<td>• 1, 1, 3, 3-propane tetraphosphonic acid, tetrasodium salt, dihydrate (PTP)</td>
</tr>
<tr>
<td>• Sodium dihydrogen phosphate, anhydrous</td>
<td>• Stannous chloride dihydrate</td>
</tr>
<tr>
<td>• Disodium monohydrogen phosphate, anhydrous</td>
<td>• Sodium hydroxide / Hydrochloric acid (for pH adjustment)</td>
</tr>
<tr>
<td>• Sorbitol E420</td>
<td>• Nitrogen</td>
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<tr>
<td>• Under nitrogen atmosphere</td>
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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
  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 \(^{(99mTc)}\) 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 administrated technetium \(^{(99mTc)}\)-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\(^{\text{®}}\) findings with labeled \(^{(99mTc)}\)WBCs
- Higher image quality Scintimun\(^{\text{®}}\) vs \(^{(99mTc)}\)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\(^{\text{®}}\) should not be used for the diagnosis of diabetic foot infection

\(^{(2)}\) Bosslet “Binding to blood cells”, Study MAb BW 250/183-BS-9 Sept 6, 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
\(^{(6)}\) Clinical trial ref 7 MN-302SZ-A, 7D-101 SZ-A
\(^{(8)}\) Clinical trial ref 7 MN-302SZ-A, 7D-101SZ-A\(^{(9)}\) (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 (EMEA) 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.

DOSE AND METHOD OF ADMINISTRATION
Scintimun® should be reconstituted with the solvent provided and then radiolabelled with sodium pertechnetate (99mTc) injection in order to obtain a clear and colourless technetium (99mTc) besilesomab injection. In adults, the recommended activity of technetium (99mTc) 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 (99mTc) 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 (99mTc)-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
EU/1/09/602/001 and EU/1/09/602/002.

DATE OF REVISION OF TEXT
11 January 2010

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

4hr

24hr

99mTc-WBCs

4hr

24hr

Fig. 1: Scintimun® and 99mTc-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
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.