SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Scintimun 1 mg kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Scintimun contains 1 mg of besilesomab.

Besilesomab is an anti-granulocyte monoclonal antibody (BW 250/183), produced in murine cells.

The radionuclide is not part of the kit.

Excipient(s) with known effect
Each vial of Scintimun contains 2 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

Scintimun: white powder
Solvent for Scintimun: white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the technetium (^{99m}Tc) besilesomab solution obtained is indicated in adults for 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.

4.2 Posology and method of administration

This medicinal product is for use in designated nuclear medicine facilities only, and should only be handled by authorised personnel.

Posology
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.

For repeated use, see section 4.4.

Elderly
No dose adjustment is required.

Renal impairment / Hepatic impairment
Formal studies have not been performed in patients with renal or hepatic impairment. However, due to the nature of the molecule and the short half-life of technetium (^{99m}Tc) besilesomab, dose adjustment is not necessary in such patients.

Paediatric population
The safety and efficacy of Scintimun in children and adolescents have not yet been established.
No data are available.

Method of administration
The radiolabelled solution should be administered intravenously as a single dose only.

This medicinal product should be reconstituted and radiolabelled before administration to the patient.
For instructions on reconstitution and radiolabelling of the medicinal product before administration, see section 12.

For patient preparation, see section 4.4.

Image acquisition
Images acquisition 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.

4.3 Contraindications

Hypersensitivity to the active substance, to other murine antibodies, to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.

Positive screening test for human anti-mouse antibody (HAMA).

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.
Since allergic reactions to the murine protein cannot be excluded, cardiovascular treatment, corticosteroids, and antihistamines must be available during administration of the product.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit.
The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Patient preparation
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.

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.

Interpretation of images
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.

After the procedure
Close contact with infants and pregnant women should be restricted during the first 12 hours after the injection.

Specific warnings

Fructose intolerance
This medicine contains 2 mg sorbitol in each vial of Scintimun.
Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

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 (see section 4.3).

Repeated use
Data on repeated dosing of Scintimun are very limited. Scintimun should only be used once in a patient's lifetime.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. . If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy
The use of besilesomab is contraindicated in pregnant women (see section 4.3).

Breast-feeding
It is not known if the product is excreted in human milk. A risk to a breast-fed child cannot be excluded.

Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted for three days and the expressed feeds discarded. These three days correspond to 10 half-lives of technetium (^{99m}Tc) (60 hours). At that time the remaining activity represents about 1/1000 of the initial activity in the body.

Close contact with infants should be restricted during the first 12 hours after the injection.

4.7 Effects on ability to drive and use machines

Scintimun has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In the most recent clinical study in which 123 patients were administered Scintimun, the most commonly reported adverse reaction was the development of anti-mouse antibodies (HAMA) in 14 % of the patients, after a single administration (16 positive over 116 assayed one and/or three months after the administration)**.**

The table below reports adverse reactions by MedDRA system organ classes. The frequencies are based on the most recent clinical trial and non interventional safety survey.

The frequency listed below is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000)
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Classes	**Adverse reactions**	**Frequency**
Immune system disorders	Anaphylactic/anaphylactoid reaction	Rare
	Hypersensitivity, including angioedema, urticaria	Uncommon
Vascular disorders	Hypotension	Common
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Rare
Investigations	Human anti-mouse antibody positive	Very common

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the frequency of these adverse reactions is not known. As the effective dose is about 6.9 mSv when the maximal recommended activity of 800 MBq is administered these adverse reactions are expected to occur with a low probability.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

България Изпълнителна агенция по лекарствата ул. „Дамян Груев“ № 8 1303 София Тел.: +359 2 8903417 уебсайт: www.bda.bg	**Danmark** Lægemiddelstyrelsen Axel Heides Gade 1 DK-2300 København S Websted: www.meldenbivirkning.dk
Ελλάδα Εθνικός Οργανισμός Φαρμάκων Μεσογείων 284 GR-15562 Χολαργός, Αθήνα Τηλ: + 30 21 32040337 Ιστότοπος: http://www.eof.gr http://www.kitrinikarta.gr	**Hrvatska** Agencija za lijekove i medicinske proizvode (HALMED) Internetska stranica: www.halmed.hr ili potražite HALMED aplikaciju putem Google Play ili Apple App Store trgovine
Κύπρος Φαρμακευτικές Υπηρεσίες Υπουργείο Υγείας CY-1475 Λευκωσία Τηλ: +357 22608607 Φαξ: + 357 22608669 Ιστότοπος: www.moh.gov.cy/phs	**Magyarország** Nemzeti Népegészségügyi és Gyógyszerészeti Központ Postafiók 450 H-1372 Budapest Honlap: www.ogyei.gov.hu elektronikus bejelentő form: https://mellekhatas.ogyei.gov.hu/ e-mail: adr.box@ogyei.gov.hu
Malta ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal	**România** Agenţia Naţională a Medicamentului şi a Dispozitivelor Medicale din România Str. Aviator Sănătescu nr. 48, sector 1 Bucureşti 011478- RO e-mail: adr@anm.ro Website: www.anm.ro
Suomi/Finland **[Finnish]** www-sivusto: www.fimea.fi Lääkealan turvallisuus- ja kehittämiskeskus Fimea Lääkkeiden haittavaikutusrekisteri PL 55 00034 FIMEA	**[Swedish]** webbplats: www.fimea.fi Säkerhets- och utvecklingscentret för läkemedelsområdet Fimea Biverkningsregistret PB 55 00034 FIMEA

4.9 Overdose

No case of overdose has been reported.

In the event of administration of a radiation overdose with technetium (^{99m}Tc) besilesomab, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent bladder voiding, and by the use of laxatives to promote faecal excretion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, inflammation and infection detection, Technetium (^{99m}Tc) compounds, ATC code: V09HA03

Mechanism of action
Besilesomab is a murine immunoglobulin of IgG1 isotype that specifically binds to NCA-95 (non specific cross-reacting antigen 95), an epitope expressed at the cell membrane of granulocytes and granulocyte precursors. Besilesomab cross-reacts with tumours expressing carcinoembryonic antigen (CEA). Besilesomab has no effect on activation of complement, granulocyte function or platelets.

Pharmacodynamic effects
At the recommended activities, it does not exert any clinically relevant pharmacodynamic effects.

Clinical efficacy
In a randomised cross-over trial comparing blinded reading of Scintimun and ^{99m}Tc-White Blood Cells (WBCs) images in 119 patients with suspected osteomyelitis, the agreement rate between the two methods was 83 % (lower 95 % confidence interval limit: 80 %). However, based on the investigator's diagnosis after one month of follow-up, Scintimun had a slightly lower specificity (71.8 %) than ^{99m}Tc-WBCs (79.5 %).

There are insufficient data on the use of Scintimun for the diagnosis of diabetic foot infection.

5.2 Pharmacokinetic properties

Distribution
Whole blood concentration-time radioactivity curves show a two-phase course, which can be subdivided into an early phase (0-2 h) and a late phase (5-24 h). After correcting for the decay of radionuclide, the calculated half-life of the early phase is 0.5 h whereas the late phase shows a half-life of elimination of 16 h.

Organ uptake
Six hours after injection, about 1.5 % of the whole body radioactivity is found in the liver whereas about 3.0 % is found in the spleen. Twenty-four hours after injection, the percentages of radioactivity are 1.6 % in the liver and 2.3 % in the spleen.

Non pathological unusual accumulations may be observed in the spleen (up to 6 % of the patients), in the bowel (up to 4 % of the patients), in the liver and bone marrow (up to 3 % of the patients), and in the thyroid and kidneys (up to 2 % of patients).

Elimination
Measurement of radioactivity levels in urine shows that up to 14 % of the administered activity is excreted via the bladder during the 24 h post-injection. The low renal clearance of activity (0.2 L/h for a glomerular filtration rate around 7 L/h) indicates that the kidney is not the major route of besilesomab elimination.

5.3 Preclinical safety data

Preclinical toxicity and safety studies were performed using commercial kits reconstituted with decayed technetium (^{99m}Tc) and thus the effect of radiation has not been assessed.

Preclinical data obtained with the non-radioactive compound reveal no special hazard for humans based on conventional studies of safety pharmacology, single-dose and repeated-dose toxicity, although antimurine antibodies were found in all dose groups (including controls) in a repeated-dose study in monkeys. Genotoxicity studies conducted to test for potentially genotoxic impurities were also negative. Long-term carcinogenicity studies and toxicity to reproduction have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Scintimun vial:
Sodium dihydrogen phosphate, anhydrous
Disodium monohydrogen phosphate, anhydrous
Sorbitol E420
Under nitrogen atmosphere

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life

3 years.
After radiolabelling: 3 hours.
Do not store above 25 °C after radiolabelling.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and radiolabelling of the medicinal product, see section 6.3.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Scintimun vial:
15 mL, colourless, type I glass vial, closed with chlorobutyl rubber stopper and aluminium crimped capsule (green) containing 5.02 mg of powder.

Solvent for Scintimun
15 mL, colourless, type I glass vial, closed with chlorobutyl rubber stopper and crimped aluminium capsule (yellow) containing 2.82 mg of powder.

Pack sizes:
Kit of one multidose vial of Scintimun and one vial of solvent.
Kit of two multidose vials of Scintimun and two vials of solvent.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General warning
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Contents of the vial are intended only for use in the preparation of technetium(^{99m}Tc) besilesomab and are not to be administered directly to the patient without first undergoing the preparative procedure.

For instructions on reconstitution and radiolabelling of the medicinal product before administration, see sections 12.

If at any time in the preparation of this product the integrity of this vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before reconstitution is not radioactive. However, after sodium pertechnetate (^{99m}Tc) is added, adequate shielding of the final preparation must be maintained.

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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/602/001
EU/1/09/602/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 January 2010
Date of latest renewal: 26 August 2014

10. DATE OF REVISION OF THE TEXT

11/2024

11. DOSIMETRY

Technetium (^{99m}Tc) is produced by means of a (^{99}Mo/^{99m}Tc) generator and decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6.02 hours to technetium (^{99}Tc) which, in view of its long half-life of 2.13 x 10^5 years can be regarded as quasi stable.

For each organ, or group of organs, the absorbed doses have been calculated using the methodology developed by the MIRD (Medical Internal Radiation Dose).

The effective dose has been calculated by using the absorbed doses determined for each individual organ, taking into account the weighting factors (radiation and tissue) to use according to the recommendations of the ICRP (International Commission of Radiological Protection, Publication 103).

Table 1: Values of the absorbed doses calculated for the individual male and female of reference.

Organ	**mSv/MBq**	
	Reference male	**Reference female**
Brain	0.00236	0.00312
Heart	0.00495	0.00597
Colon	0.00450	0.00576
Stomach	0.00445	0.00535
Liver	0.0100	0.0126
Small Intestine	0.00480	0.00575
Bone marrow (red)	0.0242	0.0229
Muscles	0.00317	0.00391
Ovaries		0.00594
Pancreas	0.00690	0.00826
Skin	0.00178	0.00216
Lungs	0.0125	0.0160
Spleen	0.0271	0.0324
Kidney	0.0210	0.0234
Breast		0.00301
Adrenal	0.00759	0.00937
Testis	0.00182	
Thymus	0.00351	0.00423
Thyroid	0.00279	0.00321
Bone	0.0177	0.0227
Uterus		0.00501
Gallbladder	0.00591	0.00681
Bladder	0.00305	0.00380
Whole body	0.00445	0.00552
Effective Dose 0.00863 mSv / MBq		

The effective dose resulting from the administration of an activity of 800 MBq for an adult weighing 70 kg is 6.9 mSv.
For an administered activity of 800 MBq the typical radiation dose to the target organ bone is 14.2 mGy and the typical radiation doses to the critical organs, bone marrow, spleen and kidneys are 19.4 mGy, 21.7 mGy, and 16.8 mGy respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Scintimun is a sterile powder containing 1 mg of besilesomab per vial Scintimun.

Withdrawals should be performed under aseptic conditions. The vials must not be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.
If the integrity of this vial is compromised, the product should not be used

Method of preparation

To ensure the highest radiolabelling efficiency:

- Radiolabelling is performed using freshly eluted sodium pertechnetate (^{99m}Tc).
- Eluates should only be taken from a technetium (^{99m}Tc)-generator that has been eluted within the past 24 hours (i.e. with less than 24 h in-grow).
- The first eluate taken from a technetium (^{99m}Tc)-generator that has not been eluted over the weekend must NOT be used.

Procedure

1. Take a vial of Solvent for Scintimun (yellow crimped aluminium capsule) from the kit. Disinfect the septum and allow drying. Using a syringe, introduce through the rubber seal 5 mL of 0.9% sodium chloride solution. Without removing the needle, withdraw an equivalent volume of air in order to avoid excess pressure in the vial. Shake smoothly.
2. After complete dissolution, disinfect the septum and allow drying. Transfer **1 mL** of this solution with a hypodermic syringe into a vial of Scintimun (green crimped aluminium capsule). Without removing the needle, withdraw an equivalent volume of air in order to avoid excess pressure in the vial. Swirl carefully; the content of the vial of Scintimun will dissolve within one minute (DO NOT shake).
3. After 1 min, check that the content of the vial of Scintimun has completely dissolved. Place the vial of Scintimun in an appropriate lead shielding container. Disinfect the septum and allow drying. Using a hypodermic syringe, introduce through the rubber seal **2-7 mL** of pertechnetate (^{99m}Tc) (the eluate complies with the requirements of current Eur. Ph.). Without removing the needle, withdraw an equivalent volume of air in order to avoid excess pressure in the vial. Swirl carefully to mix the whole solution (DO NOT shake). The activity must be between **400 and 1800 MBq** depending on the volume of pertechnetate (^{99m}Tc). The total volume in the vial of Scintimun equals 3 to 8 mL.
4. Fill in the enclosed label and fix it to the radiolabelled solution.
5. 10 min after the addition of pertechnetate (^{99m}Tc) the solution is ready for injection.

Notes on the instructions

- Solvent for Scintimun must NEVER be radiolabelled first and then added to Scintimun.
- The final radiolabelled injection solution must be protected from oxygen.

After reconstitution with the solvent provided and the radiolabelling with sodium pertechnetate (^{99m}Tc) injection, the resulting clear and colourless solution for injection of technetium (^{99m}Tc)-besilesomab has a pH of 6.5-7.5.

Quality control

The radiochemical purity of the final radiolabelled preparation can be tested according to the following procedure:

Method

Instant thin layer chromatography or paper chromatography.

Materials and reagents

- Adsorbent: strips (2.5 x 20 cm) for thin layer chromatography coated with silica gel (ITLC-SG) or for paper chromatography (RBM-1). Trace a starting line 2.5 cm from the bottom of the paper strip.
- Solvent: methyl ethyl ketone (MEK)
- Containers: appropriate containers such as chromatography tank or 1 000 mL Erlenmeyer flasks.
- 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 shielding.

1. Introduce the solvent into the chromatography tank to a depth of approximately 2 cm. Cover the tank and allow to equilibrate for at least 5 minutes.
2. Apply a spot (2 µL) of the radiolabelled solution to the starting line of the ITLC-SG or RBM-1 paper strip using a syringe and a needle.
3. Introduce the ITLC-SG or RBM-1 paper strip immediately into the chromatography tank using forceps to avoid formation of pertechnetate (^{99m}Tc) due to oxygen. DO NOT let the spot dry.
4. When the solvent has reached the top of the strip (about 10 minutes), use the forceps to remove the strip and dry in the air.
5. Cut the strip in two separate parts at Rf = 0.5.
6. Separately count each cut part of the strip and record the obtained values (use an appropriate detection apparatus with a constant counting time, and known geometry and background noise).
7. Calculations
   The radiochemical purity corresponds to the percentage of bound technetium (^{99m}Tc) and is calculated as follows after correcting data for background noise:

   % bound technetium (^{99m}Tc) = 100 % - % free Technetium (^{99m}Tc)

   Where, % free technetium (^{99m}Tc) $\frac{\text{Activity of cut strip from Rf 0.5 to Rf 1.0}}{\text{Total activity of strip}}$ x 100

8. The radiochemical purity (the percentage of bound Technetium (^{99m}Tc)) must be more than or equal to 95 %.
9. The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.