ANNEX I

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 the national reporting system listed in Appendix V.

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

{MM/YYYY}

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 2.13×10^5 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 http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Glycotope Biotechnology GmbH
Czerny-Ring, 22
69115 Heidelberg
GERMANY

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder shall ensure that, at launch, all physicians experienced in nuclear medicine who are expected to prescribe/use Scintimun are provided with a Direct Healthcare Professional Communication (DHPC), which includes information regarding potential risks of human anti-mouse antibody (HAMA) generation, hypersensitivity reactions and risks of acute hypotension, as agreed by CHMP.

The DHPC also includes 3 copies of a Patient Alert Card completed by the Healthcare Professional and provided to each patient.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

contains Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Scintimun 1 mg kit for radiopharmaceutical preparation
besilesomab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of Scintimun contains 1 mg of besilesomab

3. LIST OF EXCIPIENTS

Scintimun
Excipients: Sodium dihydrogen phosphate anhydrous, disodium monohydrogen phosphate anhydrous, sorbitol, under nitrogen atmosphere.

Solvent for Scintimun
1, 1, 3, 3-propane tetraphosphonic acid tetrasodium salt dihydrate, stannous chloride dihydrate, sodium hydroxide, hydrochloric acid, nitrogen.

Read the leaflet for further information before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Kit for radiopharmaceutical preparation

Contains one multidose vial Scintimun and one vial solvent for Scintimun
Contains two multidose vials Scintimun and two vials solvent for Scintimun

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use

Reconstitute Scintimun with its solvent first and then radiolabel with a sodium pertechnetate (^{99m}Tc) solution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 hours after radiolabelling.

9. SPECIAL STORAGE CONDITIONS

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

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

Do not store the reconstituted and radiolabelled product above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of radioactive waste in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/602/001 one multidose vial Scintimun and one vial solvent for Scintimun
EU/1/09/602/002 two multidose vials Scintimun and two vials solvent for Scintimun

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL Scintimun

no Blue Box included

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Scintimun 1 mg kit for radiopharmaceutical preparation
Besilesomab
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

Use within 3 hours after radiolabelling.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg

6. OTHER

CIS bio international

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL Solvent for Scintimun

no Blue Box included

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Scintimun

2. METHOD OF ADMINISTRATION

Not intended for direct application to patients.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.82 mg

6. OTHER

CIS bio international

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Additional label after reconstitution and radiolabelling with sodium pertechnetate (^{99m}Tc) solution

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

(^{99m}Tc)- Scintimun

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

^{99m}Tc

MBq
ml
hour/date

6. OTHER

CIS bio international

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Scintimun 1 mg kit for radiopharmaceutical preparation
besilesomab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or the nuclear medicine specialist who will supervise the procedure.
- If you get any side effects, talk to your nuclear medicine doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Scintimun is and what it is used for

Scintimun is a medicine containing an antibody (besilesomab) used to target specific cells called granulocytes (a type of white blood cells involved in the inflammation process) in your body.
Scintimun is used for the preparation of a radioactive solution for injection of technetium(^{99m}Tc)-besilesomab. Technetium(^{99m}Tc) is a radioactive element allowing the organs where besilesomab accumulates to be seen using a special camera.

This medicine is a radiopharmaceutical product for diagnostic use only in adults.
After injection into your vein, your doctor can obtain pictures (scans) of your organs that give more information about the detection of sites of inflammation and/or infection. However Scintimun should not be used for the diagnosis of diabetic foot infection.
The use of Scintimun does involve exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

2. What you need to know before you are given Scintimun

Scintimun must not be used:
- if you are allergic to besilesomab, to antibody from mouse origin or any other antibodies, or to sodium pertechnetate (^{99m}Tc) solution or any of the other ingredients of this medicine (listed in section 6).
- if you have a positive response to a test detecting human anti-mouse antibodies (HAMA test). Ask your doctor if you are not sure.
- if you are pregnant.

Warnings and precautions
Talk to the nuclear medicine specialist before using Scintimun**:**
- if you have previously been administered Scintimun, because you should only be administered Scintimun once in your lifetime. If you are not sure if you have been given this medicine before, please let your doctor know.
- if you have had a scintigraphy with technetium in the last 2 days.
- if you have a tumoral pathology involving a secretion of carcino-embryonic antigen (CEA) which could interfere with this investigation.
- if you have any blood disease.
- if you are breast-feeding.

Before administration of Scintimun
In order to obtain images of best quality and to reduce the radiation exposure of your bladder, you should drink sufficient amounts and empty your bladder prior to and after the scintigraphic examination.

Children and adolescents
This medicine is not recommended for use in patients below 18 years of age because the safety and efficacy of the product have not been established.

Other medicines and Scintimun
Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, since they may interfere with the interpretation of the images.
Medicines reducing inflammation and medicines affecting the production of your blood cells (such as corticosteroids or antibiotics) may affect the results of your examination.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your nuclear medicine doctor for advice before you are given this medicine.

You must inform the nuclear medicine doctor before the administration of Scintimun if there is a possibility you might be pregnant, if you have missed your period or if you are breast-feeding. When in doubt, it is important to consult your nuclear medicine doctor who will supervise the procedure.

If you are pregnant you must not be given Scintimun.
Investigations in nuclear medicine may involve a risk to the unborn.

If you are breast-feeding you must stop breast-feeding for 3 days after your injection and the expressed milk should be discarded. If you wish, you can express and store your breast milk **before** your injection. This will protect your child from the radiation that may be present in your breast milk.
Please ask your nuclear medicine doctor when you can resume breast-feeding.
Moreover you must avoid close contact with your child during the first 12 hours after the injection.

Driving and using machines
It is considered unlikely that Scintimun will affect your ability to drive or to use machines.

Scintimun contains sorbitol and sodium
This medicine contains 2 mg sorbitol in each vial of Scintimun. Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.
You must tell your doctor before receiving this medicine if you have HFI.

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

3. How Scintimun is given

There are strict laws on the use, handling and disposal of radiopharmaceutical products. Scintimun will only be used in special controlled areas. This product will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this product and will keep you informed of their actions.

The nuclear medicine doctor supervising the procedure will decide on the quantity of technetium(^{99m}Tc)- besilesomab to be used in your case. It will be the smallest quantity necessary to get the desired information.
The quantity to be administered usually recommended for an adult ranges from 400 to 800 MBq (megabecquerel, the unit used to express radioactivity).

Administration of Scintimun and conduct of the procedure
Scintimun is administered intravenously.
A single injection into a vein in your arm is sufficient to conduct the test your doctor needs.

Duration of the procedure
Your Nuclear medicine doctor will inform you about the usual duration of the procedure.

After administration of Scintimun
Because you could emit radiation especially harmful to young children during the first 12 hours after the injection, you should avoid close contact with young children and pregnant women during this period of time.

The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.

If you have been given more Scintimun than you should
An overdose is unlikely because injection is prepared as a single dose by the hospital personnel, under strictly controlled conditions. However, in the case of an overdose, you will be asked to drink plenty of water and to take laxatives to increase the elimination of the product from your body.

Should you have any further questions on the use of Scintimun, please ask the nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

This radiopharmaceutical will deliver low amounts of ionising radiation associated with the least risk of cancer and hereditary abnormalities.

About 14 out of 100 patients having this injection have been found to produce antibodies in their blood reacting against the antibody present in Scintimun. This may increase the risk of allergic reactions in case of repeated administration of Scintimun. Therefore you should not receive Scintimun a second time.
In case of allergic reaction you will receive appropriate treatment from your doctor.

Possible side effects are listed in the order of their frequency below:

Very common (may affect more than 1 in 10 people):
Development of human anti-mouse antibodies reacting against the antibody in Scintimun (antibody of the mouse cells) with a risk of allergic reaction

Common (may affect up to 1 in 10 people):
Low blood pressure

Uncommon (may affect up to 1 in 100 people):
Allergic reaction, including swelling of the face, hives (urticaria)

Rare (may affect up to 1 in 1,000 people):
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Muscle or joint pain

Reporting of side effects
If you get any side effects, talk to your doctor or the specialist in nuclear medicine. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How Scintimun is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulation on radioactive materials.

6. Contents of the pack and other information

What Scintimun contains
- The active substance is besilesomab (anti-granulocyte monoclonal antibody from mouse origin).
  One vial of Scintimun contains 1 mg of besilesomab.
- The other ingredients are (see section 2 “Scintimun contains sorbitol and sodium”):

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

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

What Scintimun looks like and contents of the pack
Scintimun is a kit for radioactive preparation.
The vial of Scintimun contains a white powder.
The vial of solvent for Scintimun contains a white powder.

The kit contains one or two multidose vials of Scintimun with one or two vials of solvent.

Not all pack-sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
CIS bio international
B.P. 32
F-91192 Gif-sur-Yvette Cedex
France

This leaflet was last revised in {**MM/YYYY**}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

The following information is intended for healthcare professionals only:
The complete SmPC of Scintimun is provided as a tear-off section at the end of the printed leaflet in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.
Please refer to the SmPC.