EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2016
EMA/CHMP/39283/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC and Package Leaflet for nanocolloidal technetium (^{99m}Tc) albumin

Draft

Draft agreed by Radiopharmaceutical Drafting Group	January 2016
Adopted by CHMP for release for consultation	28 January 2016
Start of public consultation	1 February 2016
End of consultation (deadline for comments)	30 April 2016

Comments should be provided using this template. The completed comments form should be sent to radiopharmaceuticalsDG@ema.europa.eu

Keywords	***Radiopharmaceuticals, radionuclide, kit for radiopharmaceutical preparation, core SmPC, core Package Leaflet, nanocolloidal technetium (^{99m}Tc) albumin***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guideline on core SmPC and Package Leaflet for nanocolloidal technetium (^{99m}Tc) albumin

Table of contents

Executive summary

This guideline describes the information to be included in the Summary of Products Characteristics (SmPC) and package leaflet for nanocolloidal technetium (^{99m}Tc) albumin.

1. Introduction (background)

The purpose of this core SmPC and package leaflet is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of product characteristics (SmPC) for nanocolloidal technetium (^{99m}Tc) albumin[1]. This guideline should be read in conjunction with the core SmPC and package leaflet for Radiopharmaceuticals, the QRD product information templates and the guideline on Summary of Product Characteristics.

This Core SmPC has been prepared on the basis, and taking into account the available published scientific literature. However, any new application or extension of indications for a radiopharmaceutical product containing nanocolloidal technetium (^{99}mTc) albumin should be submitted with all the needed data in order to be valid. For any new indication that is not in the core SmPC, it should be supported by appropriate efficacy and safety data.

2. Scope

This core SmPC and package leaflet covers nanocolloidal technetium (^{99m}Tc) albumin.

3. Legal basis

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

4. Core SmPC and Package Leaflet for nanocolloidal technetium (^{99m}Tc) albumin

[1]Concept paper on the harmonisation and update of the clinical aspects in the authorised conditions of use for radiopharmaceuticals and other diagnostic medicinal products (EMEA/CHMP/EWP/12052/2008)

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

< ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.>

1. NAME OFTHE MEDICINALPRODUCT

{(Invented) name strength kit for radiopharmaceutical preparation}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains [...] mg nanocolloidal human albumin.

At least <XX>% of human albumin colloidal particles have a diameter ≤ {XX} nm.
{(Invented) name} is prepared from human serum albumin derived from human blood donations tested according to the EEC Regulations.

The radionuclide is not part of the kit.

- Excipient(s) with known effect:

[Product specific]

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
[Appearance product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the product is indicated for:

- Lymphatic scanning to demonstrate the integrity of the lymphatic system and to differentiate venous from lymphatic obstruction.
- Sentinel node detection lymphoscintigraphy and intraoperative detection for radio-guided biopsy in melanoma, breast carcinoma, penile carcinoma, squamous cell of the oral cavity and vulvar carcinoma.

4.2 Posology and method of administration

The medicinal product should only be administered by trained healthcare professionals with technical expertise in performing and interpreting sentinel lymph node mapping procedures.

Posology

Adults

Recommended activities are as follows:

- Lymphatic scanning:

The recommended activity by single or multiple injections by subcutaneous (interstitial) is from 20 to 110 MBq per injection site.

For sentinel node detection: The dose depends on the time interval between injection and the image acquisition or the surgery.

- Melanoma: 10 to 120 MBq in several doses by intradermal peritumoural injection.
- Breast carcinoma: 5-200 MBq in several doses each from 5-20 MBq to be administered by intradermal or subdermal or periareolar injection (superficial tumours) and by intratumoural or peritumoral injection (deep tumours).
- Penile carcinoma: 40-130 MBq in several doses each of 20 MBq to be administered intradermally around the tumour.
- Squamous cell carcinoma of the oral cavity:
- 15-120 MBq to be administered by single or multiple intratumoural (superficial tumours) or peritumoural injections (deep tumours).
- Vulvar carcinoma:
- 60-120 MBq to be administered by peritumoural injection.

Renal impairment/Hepatic impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Paediatric population
The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the benefit/risk ratio in this patient group. The activity for children may be calculated from the recommended range of adult activity and adjusted according to body weight. The Paediatric Task Group of the European Association of Nuclear Medicine (EANM 1990) recommends to calculate the administered activity from the body weight according to the following table.

Fraction of adult dose:

3 kg=0.10	22 kg=0.50	42 kg=0.78
4 kg=0.14	24 kg=0.53	44 kg=0.80
6 kg=0.19	26 kg=0.56	46 kg=0.82
8 kg=0.23	28 kg=0.58	48 kg=0.85
10 kg=0.27	30 kg=0.62	50 kg=0.88
12 kg=0.32	32 kg=0.65	52-54 kg=0.90
14 kg=0.36	34 kg=0.68	56-58 kg=0.92
16 kg=0.40	36 kg=0.71	60-62 kg=0.96
18 kg=0.44	38 kg=0.73	64-66 kg=0.98
20 kg=0.46	40 kg=0.76	68 kg=0.99

For use in children, it is possible to dilute the product before administration, see section 12 .

Method of administration:

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

- Lymphatic scanning: the product is given by single or multiple subcutaneous injections, depending on the anatomical areas to be investigated and upon the time interval between injection and imaging. The injected volume should not exceed 0.2-0.3 ml. A volume more than 0.5 ml per injection site must not be applied.

The subcutaneous injection should be given after checking by aspiration that a blood vessel has not been inadvertently punctured.

- Sentinel node detection:
    - Melanoma: the activity is administered in four doses surrounding the tumor/scar, by injecting volumes of 0.1-0.2 ml.
    - Breast carcinoma: a single injection in small volume (0.2 mL) is recommended. Multiple injections may be used in particular circumstances/conditions. When using superficial injections, large volumes of injectate may interfere with normal lymphatic flow; therefore, volumes of 0.05–0.5 mL are recommended. With peritumoral injections, larger volumes (e.g. 0.5–1.0 mL) may be used.
    - Penile carcinoma: the dose should be administered thirty minutes after local spray anaesthesia by intradermal injection into three or four depots of 0.1 ml around the tumour of 0.3–0.4 ml. For large tumours not restricted to the glans, the product can be administered in the prepuce.
    - Squamous cell carcinoma of the oral cavity: the activity is administered in two to four doses surrounding the tumor/scar in a total volume of 0.1-1.0 ml.
    - Vulvar carcinoma: the activity is administered in four peritumoural doses in a total volume of 0.2 ml

This product is not intended for regular or continuous administration.

<u>Image acquisition</u>

- Lymphatic scanning

When imaging the lower limbs, dynamic images are taken immediately following injection and static imaging 30-60 minutes later.
In parasternal lymph scanning, repeated injections and additional images may be required.

- Sentinel node detection

Melanoma: Lymphoscintigraphic images are acquired starting after injection and regularly thereafter until the sentinel lymph node is visualized.

Breast carcinoma: Scintigraphic images of breast and axillary region can be acquired by early detections (15-30 minutes) and late detections (3-18 hours) after injection.

Squamous cell carcinoma of the oral cavity: dynamic acquisition for 20 to 30 minutes starting immediately after injection. Two or three simultaneous static images from one or both sides in the anterior and lateral projections are recommended. Static images can be repeated at 2 hours, 4–6 hours, or just before surgery. SPECT imaging may improve the identification of sentinel lymph nodes, especially close to the injection site. Repeat injection and imaging may be considered; however, proceeding to neck dissection is preferred in order to avoid a false-negative sentinel lymph node.

Penile carcinoma: dynamic imaging can be performed immediately after injection and followed by static imaging at 30 minutes, 90 minutes, and 2 hours post-injection by using dual-head gamma camera.

Vulvar carcinoma: image acquisition is to be obtained starting after the injection and every 30 min thereafter until the sentinel node(s) is visualized. The injection and images can be carried out the day before surgery or on the day of surgery. Planar images acquisition for 3 – 5 minutes in anterior and lateral

views, and subsequent SPECT/CT images, are recommended.

For patient preparation, see section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance(s), to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.
In particular, the use of nanocolloidal technetium (^{99m}Tc)-albumin is contraindicated in persons with a history of hypersensitivity to products containing human albumin.
In patients with complete lymph obstruction lymph node scintigraphy is not advisable because of the danger of radiation necroses at the site of injection.
During pregnancy, lymphoscintigraphy involving the pelvis is strictly contraindicated due to the accumulation in pelvic lymph nodes.

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
The possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/ anaphylactoid reactions should always be considered.
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.

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.

Paediatric population
For information on the use in paediatric population, see sections 4.2.
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation.

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

Specific warnings
[*Product specific*]

It is strongly recommended that every time that {name of product} is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection, and the inclusion of effective manufacturing steps for the

inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

Lymphoscintigraphy is not advised in patients with total lymphatic obstruction because of the potential radiation hazard at injection sites. The subcutaneous injection must be made without pressure into loose connective tissue.

<This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.>

For precautions with respect to environmental hazard are in section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

<No interactions studies have been performed in adults or children.>
Iodinated contrast media used in lymphoangiography may interfere with lymphatic scanning using nanocolloidal technetium (^{99m}Tc) albumin.

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
Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus.

During pregnancy, lymphoscintigraphy involving the pelvis is strictly contraindicated due to the accumulation in pelvic lymph nodes (see section 4.3).

Breast-feeding
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, 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, breastfeeding should be interrupted for 13 hours and the expressed feeds discarded.

Fertility
No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

<{(invented) name} has no or negligible influence on the ability to drive and use machines.>
<No studies have been performed on the ability to drive and use machines.>

4.8 Undesirable effects

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 0.8 mSv when the maximal recommended activity of 200 MBq is administered these adverse reactions are expected to occur with a low probability.

During the evaluation of side effects the following frequency data are taken as a basis:

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)
Very rare (<1/10,000)
not known (cannot be estimated form the available data)

Immune system disorders	
Frequency not known (cannot be estimated from the available data).	Protein allergic (hypersensitive) reaction
Frequency not known (cannot be estimated from the available data).	Hypersensitivity reactions (including very rare life-threatening anaphylaxis).
Very rare	local reactions, rash, itching, vertigo, hypotension

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.

For safety with respect to transmissible agents see section 4.4.

4.9 Overdose

In the event of administration of a radiation overdose with nanocolloidal technetium (^{99m}Tc) albumin no practical measure can be recommended to satisfactorily diminish tissue exposure as the label is poorly eliminated in urine and faeces.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Technetium (^{99m}Tc), particles and colloids, ATC code: V09DB01

Pharmacodynamic effects

At the chemical concentrations used for diagnostic examinations, nanocolloidal technetium (^{99m}Tc) albumin does not appear to have any pharmacodynamics activity.

Pharmacokinetic properties
At the chemical concentrations and activities used for diagnostic examinations, nanocolloidal technetium (^{99m}Tc) albumin do not appear to have any pharmacodynamic activity.

Distribution
{(Invented) name} is a nano-sized colloidal product produced from human serum albumin.

Reticuloendothelial cells in liver, spleen as well as in bone marrow are responsible for blood clearance after intravenous injection. A small fraction of technetium (99mTc) radioactivity passes through kidneys and is eliminated in urine.

Organ uptake
The maximum concentration in the liver and spleen is reached after about 30 minutes, but in the bone marrow after only 6 minutes.
The proteolytic breakdown of the colloid begins immediately after its uptake by the RES, the products of degradation being excreted through the kidneys into the bladder.
After subcutaneous injection into connective tissue, 30-40% of the administered nanocolloidal technetium (^{99m}Tc) albumin particles are filtered into lymphatic capillaries whose main function is the drainage of proteins from the interstitial fluid back into the blood pool.
The technetium-99m albumin nano-sized colloidal particles are then transported along the lymphatic vessels to regional lymph nodes and main lymphatic vessels, and are finally trapped into the reticular cells of functionary lymph nodes.

Elimination
A fraction of the injected dose is phagocytized by histiocytes at the injection site. Another fraction appears in the blood and accumulates mainly in the reticuloendotelial system of the liver, spleen and bone marrow; faint traces are eliminated via the kidneys.

Half-life
[State biological half-life and effective half-life (including biological and physical half-lives)]

5.1 Preclinical safety data

Toxicological studies with mice and rats have demonstrated that with a single intravenous injection of 800 mg and 950 mg in mice and rats respectively no deaths and no gross pathological changes at necropsy were observed.. No local reactions were observed in either mice or rats following subcutaneous injection of 1g nanocolloidal albumin particles/kg body weight with 0.9% saline injection.

These doses correspond to the contents of 50 vials per kg body weight, which is the 3,500-fold compared to the maximum human dose.

This medicinal product is not intended for regular or continuous administration.

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

Reproductive toxicity studies are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific]

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6 and 12.

6.3 Shelf life

[Product specific]

After radiolabelling: [...] hours.

Do not store above [...]°C after radiolabelling.

6.4 Special precautions for storage

[Product specific].

< Store the vials 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

[Product specific]

<Single> <Multidose> vial.

<Not all pack sizes may be marketed>

6.6 Special precautions for disposal and other handlings

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 nanocolloidal technetium (^{99m}Tc) albumin and are not to be administered directly to the patient without first undergoing the preparative procedure.

For instructions on radiolabelling of the medicinal product before administration, see section 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 extemporary preparation is not radioactive. However, after reconstitution with *sodium pertechnetate (^{99m}Tc), Ph. Eur.* 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 spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

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

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OFTHE AUTHORISATION

10. DATE OF REVISION OFTHE TEXT

11. DOSIMETRY

Technetium-99m 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 (99Tc) which, in view of its long half-life of 2.13 x 105 years can be regarded as almost stable.
The data listed below are from ICRP 53 and give the absorbed dose following intravenous administration with effective dose calculated according to the methodology of ICRP 60 assuming that, due to the short radioactive half-life of ^{99m}Tc, no excretion or redistribution occurs.

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	0.01	0.015	0.021	0.027	0.041
Bladder wall	0.00091	0.0014	0.0025	0.0052	0.0085
Bone surfaces	0.0079	0.011	0.017	0.029	0.06
Breast	0.0025	0.0025	0.0044	0.0069	0.012
GI-tract					
Stomach wall	0.006	0.0081	0.013	0.021	0.034
Small intestine	0.0043	0.0051	0.0089	0.014	0.024
Upper large intestine	0.0055	0.0068	0.012	0.02	0.033
Lower large intestine	0.0018	0.0022	0.0038	0.0058	0.01
Kidneys	0.0097	0.0011	0.017	0.024	0.035
Liver	0.074	0.092	0.14	0.19	0.34
Lungs	0.0054	0.0074	0.01	0.014	0.024
Ovaries	0.0023	0.003	0.0049	0.0077	0.013
Pancreas	0.012	0.017	0.025	0.037	0.058
Bone marrow (red)	0.015	0.02	0.03	0.051	0.1
Spleen	0.077	0.11	0.16	0.25	0.45
Testes	0.00048	0.00057	0.00097	0.0018	0.0036
Thyroid	0.00069	0.0011	0.0017	0.0029	0.0054
Uterus	0.0018	0.0024	0.0042	0.007	0.013

Other tissue	0.0027	0.0033	0.0047	0.007	0.012
Effective Dose (mSv/MBq)	**0.0099**	**0.013**	**0.02**	**0.03**	**0.053**

The effective dose resulting from the administered activity of 500 MBq for an adult weighing 70 kg is about 4.95 mSv. For an administered activity of 500 MBq the typical radiation dose to the target organ (red bone marrow) is 7.5 mGy and the typical radiation dose to the critical organ (liver) is 37 mGy.
In the case of subcutaneous administration for sentinel node lymphoscintigraphy it can general be assumed that approximately 20% of the injected dose is absorbed systemically and the dosimetry data presented above can be scaled accordingly.

It is assumed that the dose to the injection site, which varies greatly with location, injected volume, number of injections and retention, can be ignored due to the relatively low radiosensitivity of skin and the small contribution this makes to the overall effective dose. In this case the effective dose resulting from the administered activity of 110 MBq for an adult weighing 70 kg is about 0.22 mSv.

In the case of breast sentinel node lymphoscintigraphy the data listed below (ICRP 106) assumes no leakage occurs and the absorbed dose to the remaining breast is equal to the dose to the lungs.

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**			
	6 h to removal		**18 h to removal**	
	Adult	**15 years**	**Adult**	**15 years**
Adrenals	0.00079	0.00093	0.0014	0.0016
Bladder	0.000021	0.000039	0.000036	0.000068
Bone surfaces	0.0012	0.0015	0.0021	0.0026
Brain	0.000049	0.000058	0.000087	0.0001
Breast (remaining)	0.0036	0.0039	0.0064	0.0069
Gall bladder	0.00053	0.00072	0.00093	0.0013
GI-tract				
Stomach	0.0013	0.00092	0.0023	0.0016
Small Intestine	0.00015	0.00011	0.00027	0.0002
Colon	0.00019	0.000083	0.00033	0.00014
(Upper large intestine	0.00028	0.00012	0.00049	0.0002
(Lower large intestine	0.00007	0.000038	0.00012	0.000066
Heart	0.0041	0.0052	0.0071	0.0091
Kidneys	0.00031	0.00042	0.00054	0.00073
Liver	0.0011	0.0014	0.0019	0.0024
Lungs	0.0036	0.0039	0.0064	0.0069
Muscles	0.00066	0.00083	0.0012	0.0015
Oesophagus	0.0036	0.005	0.0062	0.0087
Ovaries	0.000041	0.000048	0.000071	0.000083
Pancreas	0.00097	0.0011	0.0017	0.002
Bone marrow (red)	0.0086	0.00092	0.0015	0.0016
Skin	0.0012	0.0014	0.0021	0.0024
Spleen	0.00068	0.00083	0.0012	0.0015
Thymus	0.0036	0.005	0.0062	0.0087
Thyroid	0.00047	0.00062	0.00082	0.0011

Uterus	0.000041	0.000064		0.000071	0.00011
Remaining organs	0.00066	0.00083		0.0012	0.0015
Effective dose (mSv/MBq)	**0.0012**	**0.0014**		**0.002**	**0.0024**

The effective dose resulting from the subcutaneous administration of a (maximal recommended) activity of 110 MBq with the removal of the injection site 18 hours post-injection for an adult weighing 70 kg is about 0.22 mSv.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. The vials must not be opened before 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
[Product specific]

Quality control
[Product specific]

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

B. PACKAGE LEAFLET FOR RADIOPHARMACEUTICALS

PACKAGE LEAFLET: INFORMATION FOR THE PATIENT
{(Invented) name strength Kit for radiopharmaceutical preparation}
nanocolloidal technetium (^{99m}Tc) albumin

Read all of this leaflet carefully before you will be administered this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your referring doctor or the specialist physician in Nuclear Medicine who will supervise the procedure.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your your referring doctor or the specialist physician in Nuclear Medicine who has supervised the procedure.

What is in this leaflet

1. What X is and what it is used for

This medicine is a radiopharmaceutical product for diagnostic use only.
X should be radiolabelled with 'technetium-99m' and obtained product is used for scintigraphic imaging and assessment of
- sentinel lymph nodes in tumor diseases (Sentinel Node Mapping in melanoma, breast carcinoma, penile carcinoma, squamous cell of the oral cavity and vulvar carcinoma);
- the integrity of the lymphatic system and differentiation of venous from lymphatic obstruction.

The use of technetium (99mTc) albumin nanocolloids 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 X is used

X must not be used:
- if you are allergic to X or any of the other ingredients of this medicine (listed in section 6).
- during pregnancy if you should do a lymphoscintigraphy involving the pelvis.In patients with complete lymph obstruction, lymph node scintigraphy is not advisable because of the danger of radiation necroses at the site of injection.

Warnings and precautions
Take special care with X
- if you are pregnant or believe you may be pregnant
- if you are breast-feeding
- if you suffer from kidney or liver disease

Your nuclear medicine doctor will inform you if you need to take any special precautions after using this medicine. Talk to your nuclear medicine doctor if you have any questions.

Before administration of X you should:
- drink plenty of water before the start of the examination in order to urinate as often as possible during the first hours after the study.

Children and adolescents
Talk to your nuclear medicine doctor if you are under 18 years old.

Medicines made from human blood or plasma
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.
There are no reports of virus infections with albumin manufactured to European Pharmacopoeia requirements by established processes.
It is strongly recommended that every time you receive a dose of {name of product} the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Other medicines and X

Tell your nuclear medicine doctor if you are taking/using, have recently taken/used or might take/use any other medicines since they may interfere with the interpretation of the images.
If you must have made a scan of your lymph system, talk to your doctor before your scan, if you previously have been investigated by x-ray or scan with contrast agents. This can influence the outcome.
Please ask your nuclear medicine specialist before taking any medicines.

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 advise before you are given this medicine.
You must inform the nuclear medicine doctor before the administration of X 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:
Do not use{X} during pregnancy.

<u>If you are breast-feeding</u>
Please ask your nuclear medicine doctor when you can resume breast-feeding.
Breastfeeding should be interrupted for 13 hours and the expressed milk should be discarded.

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

X contains sodium
<This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'>.

3. How X is used

There are strict laws on the use, handling and disposal of radiopharmaceutical products. X 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 X 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 5 to 200 MBq (megabecquerel, the unit used to express radioactivity), depending on …
Dosage reductions in renal or hepatic impairment are not necessary.

Use in children and adolescents
In children and adolescents, careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. The quantity to be administered will be adapted to the child's weight.

Administration of X and conduct of the procedure
X is administered subcutaneously after radiolabeling (one or more injection sites). This product is not intended for regular or continuous administration.
After injection, you will be offered a drink and asked to urinate immediately preceding the test.

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

After administration of X, you should:
- avoid any close contact with young children and pregnant women for the 13 hours following the injection
- Urinate frequently in order to eliminate the product from your body.

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 X than you should
An overdose is unlikely because you will only receive a single dose of X precisely controlled by the nuclear medicine doctor supervising the procedure. However, in the case of an overdose, you will receive the appropriate treatment. In particular, the nuclear medicine doctor in charge of the procedure may recommend that you drink plenty of fluids in order to facilitate the elimination of X from your body.
Should you have any further question on the use of X, 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.
During the evaluation of side effects the following frequency data are taken as a basis:

very common:	more than 1 patient out of 10
common:	1 to 10 patient out of 100
uncommon:	1 to 10 patient out of 1000
rare:	1 to 10 patient out of 10000
very rare:	Less than 1 patient out of 10000
not known:	frequency cannot be estimated from available data

Very rare:
slight and temporary hypersensitivity reactions, which can express symptoms as
at the administration area/skin local reactions, rush, itching
immune system disease vertigo, blood pressure decrease
When a protein-containing radiopharmaceutical such as X is administered to a patient, hypersensitivity reactions may develop, including very rare life-threatening anaphylaxis, with frequency not known.

If you get any side effects talk to your nuclear medicine doctor. 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 X 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.

The following information is intended for the specialist only.
This medicine must not be used after the expiry date which is stated on the
<label> <carton>
<bottle> <...> <after {abbreviation used for expiry date}.> <The expiry date refers to the last day of that month.>
<This medicine will not be used if it is noticed {description of the visible signs of deterioration}.>

Storage conditions:
[Product specific]

Shelf life after first opening and radiolabelling
[Product specific]

6. Contents of the pack and other information

What X contains
The active substance is nanocolloidal human albumin. One vial contains [...] microg human albumin nanocolloids. One vial contains 0.5 mg of nanocolloidal human albumin

The excipients are
[Product specific]

What X looks like and contents of the pack

The product is a kit for radiopharmaceutical preparation.

<Each vial contains white or almost white lyophilisate for preparation of an injection suspension>.

X consists of *[product specific]* which has to be dissolved in a solution and combined with radioactive technetium before use as an injection. Once the radioactive substance technetium pertechnetate (^{99m}Tc) is added to the vial, technetium (^{99m}Tc) albumin nanocolloids are formed. This solution is ready for injection.

Pack size
[Product specific]

Marketing Authorisation Holder and Manufacturer

{Name and address}
<{tel}>

<{fax}>
<{e-mail}>

<This medicinal product is authorised in the Member States of the EEA under the following names:>

This leaflet was last revised in<{month YYYY}>.
<This medicine has been given “conditional approval”.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on the medicine every year and this leaflet will be updated as necessary.>

<This medicine has been authorised under “Exceptional Circumstances”.
This means that <because of the rarity of this disease> <for scientific reasons> <for ethical reasons> it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.>

<Other sources of information>
<Detailed information on this medicine is available on the web site of {MA/Agency}>

The following information is intended for medical or healthcare professionals only:
The complete SmPC of {(Invented) name} is provided as <a separate document> <as a tear-off section at the end of 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 included in the box.