SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PULMOCIS 2 mg kit for radiopharmaceutical preparation.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 mg macroaggregated human albumin (macrosalb).

The macroaggregates number per vial is ranging between 2 x 10^6 and 4 x 10^6. In the labelled product the particle size distribution is as follows: more than 95 % of the particles are between 10 and 100 micrometers.

Produced from human serum albumin of human donors.

The radionuclide is not part of the kit.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation
White pellet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the suspension of technetium (^{99m}Tc)-albumin macroaggregates obtained is indicated in adults and paediatric population for:

- Pulmonary perfusion scintigraphy

For the diagnosis or exclusion of pulmonary embolism in patients with symptoms of pulmonary embolism and for monitoring the evolution of a pulmonary embolism;

For examinations concomitant to therapies that result in a significant reduction in the regional lung perfusion, as preoperative investigation of local pulmonary perfusion prior to (partial) lung resection, preoperative examination and progress monitoring of lung transplants and for pre-therapeutic examinations for assisting radiation therapy planning;

In combination with ventilation scintigraphy for the initial evaluation and the follow-up of patients with severe obstructive and/or restrictive pulmonary diseases;

For the diagnosis and quantification of pulmonary right-to-left shunts.

- Radionuclide venography

As an alternative to Doppler ultrasound, for radionuclide venography of the lower limbs, in combination with pulmonary perfusion scintigraphy in patients with both suspected lower limb deep vein thrombosis and pulmonary embolism.

4.2 Posology and method of administration

This medicinal product must be administered exclusively by authorised personnel (see section "General warnings" in section 6.6).

Posology

Adults
The recommended activity intravenously administered is between 40 and 150 MBq, with a middle value of 100 MBq for planar pulmonary perfusion scintigraphy and up to 200 MBq for SPECT pulmonary perfusion scintigraphy.

The average recommended number of particles for adults should fall within the range of **100,000 and 300,000**. The maximum number of particles of 700,000 per administration must not be exceeded. The minimum number of particles per dosage administered should be 100,000 in order to obtain optimal image quality.

For calculation of the amount of particles to be administered, see section 12.

For Adult and elderly patients with severe cardiovascular disease, with pulmonary hypertension accompanied by respiratory insufficiency or with a right-to-left shunt, the number of particles should be reduced between **100,000 and 200,000**.

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 risk/benefit ratio in this patient group.
The Paediatric Task Group of the EANM (2016) recommends calculation of the activity administered to the paediatric population on the basis of body weight in accordance with table 1.

The activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent multiples given in the table below.

A[MBq]administered = baseline activity x multiple

The baseline activity is 5.6 MBq. In very young children (up to 1 year) a minimum activity of 10 MBq is necessary to obtain images of sufficient quality.

Table 1: Weight-dependent correction factors in the paediatric population according to the EANM-2016 dosage card:

Weight [kg]	Multiple	**Weight [kg]**	Multiple	**Weight [kg]**	Multiple
3	1	**22**	5.29	**42**	9.14
4	1.14	**24**	5.71	**44**	9.57
6	1.71	**26**	6.14	**46**	10.00
8	2.14	**28**	6.43	**48**	10.29
10	2.71	**30**	6.86	**50**	10.71
12	3.14	**32**	7.29	**52-54**	11.29
14	3.57	**34**	7.72	**56-58**	12.00
16	4.00	**36**	8.00	**60-62**	12.71
18	4.43	**38**	8.43	**64-66**	13.43
20	4.86	**40**	8.86	**68**	14.00

The number of particles should be kept as low as possible in order to embolise no more than 0.1% of the total lung capillary vessels. The number of particles to be administered to children and adolescents is recommended to be calculated according the recommendations of the European Association of Nuclear Medicine (EANM) guidelines for lung scintigraphy in children (2007):

Weight [kg]	Maximum number of particles to be administered
<10 Kg	10,000-50,000
10-20 Kg	50,000-150,000
20-35 Kg	150,000-300,000
35-50 Kg	300,000-500,000

In case of known or suspected severe decrease of the pulmonary vascular bed (more than 50%), the number of particles to be administered should be proportionally reduced.
For evaluation of right to left shunts, the number of administered particles should be reduced to 10,000 - 20,000.

Method of administration
For multidose use.

This medicinal product should be reconstituted before administration to the patient.

For instructions on reconstitution of the medicinal product before administration, see section 12.

Precautions to be taken before handling or administering the medicinal product
The contents of the syringe must be carefully swirled once again prior to the injection, in order to achieve a uniform distribution of the particles and in order to avoid the formation of larger-sized aggregates. A thin cannula should be used in order to disperse any complexes of aggregates present.

For the same reason, blood should never be drawn up into the syringe because that induces the formation of small clots, which are presented in the scintigraphy as false positive defects because of the occlusion of the bigger arterioles. If possible, the product should not be injected via an implanted venous access device, as this can result in inadequate mixing of the radioactivity in the pulmonary artery.

After the patient has coughed and taken several deep breaths, the medicinal product is slowly injected intravenously over 3 to 5 respiratory cycles or for at least 30 seconds. Great care must be taken to see that the radioactive product does not enter the surrounding tissues and that no blood is aspirated, as otherwise there is a danger that larger complexes of aggregates will form. The patient should lie on his back during the injection or as close to this position as possible for patients with orthopnea. The pulmonary investigation can begin immediately after the injection.

If a ventilation/perfusion scintigraphy is performed, it is advised carrying out the injection in the same position in which inhalation of the radioactive inert gas or of aerosols is undertaken, i.e. preferably in the sitting position, this position being taken up at least 5 minutes beforehand. In this way, as a consequence of the better ventilation of the lungs in the sitting position, the danger of false positive results in a staggered investigation of ventilation and perfusion is avoided.

For patient preparation, see section 4.4.

Image acquisition
The pulmonary imaging can start immediately after injection.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to any of the components of the labelled product.

- Severe pulmonary hypertension.

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.

Careful caution should be taken when administering technetium (^{99m}Tc) macrosalb to patients with pulmonary hypertension, respiratory insufficiency, possible or known right-to-left cardiac shunt or pulmonary transplant patients. In these cases, technetium (^{99m}Tc) macrosalb may not be administered except after a careful benefit/risk analysis.

In order to minimise the possibility of microembolism to the cerebral and renal circulations, technetium (^{99m}Tc) macrosalb product should be administered by slow intravenous injection. The particles number must be kept as low as possible. In adults the particles number can be reduced to between 100,000 and 200,000 particles without loss of image quality for detection of perfusion defects without affecting the quality of images for the visualization of perfusion defects. Heterogeneous distribution of the radioactivity may occur when the number of particles is below 100.000 units.

Renal impairment/Hepatic impairment

Careful consideration of the benefit/risk ratio in these patients is required since an increased radiation exposure is possible (see section 4.2.).

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.

A thyroid blockade prior to application of the technetium (^{99m}Tc) macrosalb injection suspension can help to reduce the radiation exposure of the thyroid by reducing the thyroid-uptake of technetium (^{99m}Tc) pertechnetate which develops in lesser amounts by the metabolism.

After the procedure

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

Specific warnings

PULMOCIS contains human albumin. It is strongly recommended that every time that PULMOCIS 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 according to European Pharmacopoeia specifications by established processes.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium- free'.

For precautions with respect to environmental hazard, see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Changes in the biological distribution of technetium (^{99m}Tc) macrosalb may be induced by different medicinal products.

- Pharmacologic interactions may be caused by chemotherapeutic medicinal products, heparin and bronchodilators.
- Toxicological interactions may be caused by heroin, nitrofurantoin, busulfan, cyclophosphamide, bleomycin, methotrexate, methysergide.
- Pharmaceutical interactions may be caused by magnesium sulphate. Complexes of most voluminous aggregates can form after treatment with albumin macroaggregates labelled with technetium-99m in patients receiving intravenous therapy; these may pass into the pulmonary circulation.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When 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 doses 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 the foetus.

Breast-feeding

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, breastfeeding should be interrupted for 12 hours and the expressed feeds discarded.

Fertility

No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

For safety information with respect to transmissible agents, see section 4.4.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 2.2 mSv, when the maximal recommended activity of 200 MBq is administered these adverse reactions are expected to occur with a low probability.

The frequencies of undesirable effects are defined as follows:
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) and not known (cannot be estimated from the available data).

Immune system disorders
Frequency not known:
Hypersensitivity reactions such as urticaria, chills, fever, nausea, face erythema and sweating as well as impairments of cardiac and circulatory functions in the form of changes in respiration, pulse, blood pressure, chest pain and collapse which may be related to vascular occlusion.

Very rare: Serious anaphylactoid reactions including shock with possible fatal outcome have been reported. The appearance of these reactions may also not be immediate.

General disorders and administration site conditions
Frequency not known: Local allergic reactions at the injection site have been observed.

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 Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The number of MAA particles per adult patient must not exceed 1.5 x 10^6.

An administration of a very high number of particles can lead to a hemodynamically significant vascular blockage. When pronounced changes in respiration, pulse and blood pressure occur, respiratory and circulatory stabilising measures should be taken.

In the event of the administration of a radiation overdose the absorbed dose with technetium (^{99m}Tc) macrosalb to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective dose that was applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, technetium (^{99m}Tc), particles for injection.
ATC code: V09EB01

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

5.2 Pharmacokinetic properties

Distribution

Following intravenous injection of technetium (^{99m}Tc) macrosalb, temporary occlusion of pulmonary capillaries and arterioles occurs, which is proportional to the regional pulmonary blood flow at the time.

Organ uptake

The principle of perfusion scintigraphy is capillary blockade. The albumin macroaggregate particles do not penetrate the lung parenchyma (interstitial or alveolar) but remain in a temporary occlusive position in the lumen of the capillary. After intravenous injection most of the macrosalb aggregates are retained in the arterioles and capillaries of the lung at the time of first passage through the lungs. The diameter of most of the macroaggregates is between 30 and 50 micrometers. Depending on the distribution of particle sizes, roughly every 1,000,000th capillary (diameter < 20 micrometer) and every 1,000th arteriole (diameter > 20 micrometer) is temporarily occluded. The extent of the regional blockade with micro embolisms is thus directly proportional to the regional lung perfusion at the time. Larger particles can lead to occlusion of larger vessels and therefore cause artificial perfusion disturbances. Hemodynamic changes are directly linked to the particle size of the macrosalb aggregates.

Elimination

The elimination of the macroaggregate particles from the lungs takes place by mechanical fragmentation through the systolic-diastolic pressure pulses within the capillaries and by enzymatic breakdown with subsequent phagocytosis by macrophages of the reticuloendothelial system. In the context of elimination, activity accumulates in the liver and kidneys.

Liver accumulation is extremely variable; it increases over time and can become as high as approximately 25%.
With regard to elimination from the lungs, great differences exist between individuals. The particles are eliminated from the lungs with a biological half-life of about 7-20 hours. 30-45% of the injected radioactivity is excreted through the urine within 24 hours.

If a right-to-left shunt is present, a proportion of the macroaggregates moves into the general circulation system and becomes trapped there in the capillary bed. If this happens, the formation of a cerebral or renal microembolism is, for example, possible.

Renal / Hepatic impairment

The pharmacokinetics in patients with renal or hepatic impairment has not been characterised.

5.3 Preclinical safety data

Correlation exists between the size of the particles and their toxic effects.

The pathophysiologic mechanism responsible for toxicity is shown to be the increase of the pulmonary blood pressure.Toxicological studies with dogs have demonstrated that with a single IV injection of 20 to 25 mg/kg of MAA having 10 to 50 µm in diameter the first pulmonary signs of toxicity (e.g. tachypnea) were observed.

A sharp increase of the pulmonary blood pressure is noticed when 20 mg of less than 80 micrometer sized macrosalb particles are injected, where no significant pressure changes are recorded with 40 mg of less than 35 micrometer macrosalb particles.

With suspension of macrosalb particles up to 150 micrometer diameter, no blood pressure changes appear below 10 mg/kg, while larger diameter suspensions (up to 300 micrometer) typical blood pressure changes in pulmonary artery appear when the dose exceed 5 mg/kg.

Doses of 20-50 mg/kg cause sudden death from failure. A safety factor of 100 is found after injection in dogs of 14,000 particles of technetium (^{99m}Tc) macrosalb (size: 30 - 50 micrometer).

The repeated-dose toxicity studies performed in dogs show no detectable variations in the general behaviour of the animals.

No evidence of pathological changes in the main organs has been detected.

There is no evidence in the literature of teratogenic, mutagenic or carcinogenic effect of the unlabelled product.

This agent is not intended for regular or continuous administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Stannous chloride dihydrate (E 512)
Sodium chloride
Under nitrogen atmosphere (E 941)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.
The medicinal product should not come into contact with air.

6.3 Shelf life

Kit:1 year.
After radiolabelling: 8 hours. Store at 2°C – 8°C.

6.4 Special precautions for storage

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

For storage conditions after reconstituting 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

15 mL, colourless, European Pharmacopoeia type I, drawn glass vials, closed with rubber stoppers and aluminium capsules.
Pack size: 5 multidose vials.

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) macrosalb 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 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 sodium pertechnetate (^{99m}Tc), solution 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

CIS bio international
RN 306 - Saclay
B.P. 32
F-91192 Gif-sur-Yvette Cedex
FRANCE

8 MARKETING AUTHORISATION NUMBER

PL 11876/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 July 1996.
Date of latest renewal: 11 June 2010.

10 DATE OF REVISION OF THE TEXT

15/04/2019.

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.

The data listed below in table 2 are from ICRP 128 publication.

Table 2:

Organ	Absorbed dose per unit activity administered (mGy / MBq)				
	Adults	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.0068	0.0088	0.013	0.019	0.031
Bone surfaces	0.0051	0.0064	0.0091	0.014	0.026
Brain	0.00092	0.0012	0.0020	0.0032	0.0055
Breast	0.0050	0.0056	0.0099	0.014	0.021
Gall bladder wall	0.0056	0.0070	0.010	0.016	0.024
Gastrointestinal tract					
Stomach wall	0.0037	0.0052	0.008	0.012	0.020
Small intestine wall	0.0020	0.0026	0.0043	0.0068	0.012
Colon wall	0.0019	0.0026	0.0043	0.0069	0.012
(Upper large intestine wall	0.0022	0.0029	0.0050	0.0083	0.014)
(Lower large intestine wall	0.0016	0.0021	0.0033	0.0050	0.0095)
Heart wall	0.0096	0.013	0.018	0.025	0.038
Kidneys	0.0037	0.0048	0.0072	0.011	0.018
Liver	0.016	0.021	0.030	0.042	0.074
Lungs	0.066	0.097	0.13	0.20	0.39
Muscles	0.0028	0.0037	0.0052	0.0077	0.014
Oesophagus	0.0061	0.0077	0.011	0.015	0.022
Ovaries	0.0018	0.0023	0.0035	0.0054	0.010
Pancreas	0.0056	0.0075	0.011	0.017	0.029
Red marrow	0.0032	0.0038	0.0053	0.0072	0.012
Skin	0.0015	0.0017	0.0027	0.0043	0.0078
Spleen	0.0041	0.0055	0.0083	0.013	0.022
Testes	0.0011	0.0014	0.0022	0.0033	0.0062
Thymus	0.0061	0.0077	0.011	0.015	0.022
Thyroid	0.0025	0.0033	0.0057	0.0090	0.016
Urinary bladder wall	0.0087	0.011	0.014	0.016	0.030
Uterus	0.0022	0.0028	0.0042	0.0060	0.011
Remaining organs	0.0028	0.0036	0.0050	0.0074	0.013
Effective dose (mSv/MBq)	**0.011**	**0.016**	**0.023**	**0.034**	**0.063**

The effective dose resulting from the administration of a (maximal recommended) activity of 150 MBq for planar perfusion scintigraphy for an adult weighing 70 kg is about 1.7 mSv and 2.2 mSv for 200 MBq (maximum recommended dose for SPECT).

For an administered activity of 150 MBq the typical radiation dose to the target organ (the lungs) is 10 mGy and the typical radiation dose/doses to the critical organ/organs (adrenal glands, bladder wall, liver, pancreas and spleen) are 1.0, 1.3, 2.4, 0.8 and 0.6 mGy, respectively.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions.
The vials must never 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.

Estimation of volume and activity of Sodium Pertechnetate (^{99m}Tc) in relation with the number of macrosalb particles and activity per dose

According to section 4.2. ”Posology and method of administration” it is necessary to define the volume and radioactivity of the Sodium Pertechnetate (^{99m}Tc) solution to be added to the kit in relation to the activity and to the number of particles of macroaggregates to be administered to adults or pediatric patients.

The following procedure and formulations should be considered on this purpose.

1. The first step consists in the determination of the labelling volume of the macroaggregate, to be injected per dose.

   The calculation formula is the following:

$$\text{Labelling volume} = \frac{\text{Number of macroaggregate particles per vial x Volume to inject}}{\text{Number of macroaggregate particles to be injected per dose}}$$

2. The second step consists in the determination of the total activity to add to the vial as a function of the activity to be injected and the volume of the eluate.

   The calculation formula is the following:

$$\text{Radioactivity for the labelling} = \frac{\text{Activity to be injected x Labelling volume}}{\text{Volume to be injected}}$$

Table 3: Guide for the calculation of the volume and activity of the pertechnetate solution (^{99m}Tc) to be added depending on the activity and the number of macro-aggregates per dose, in adults or paediatric patients.

Results are given for the range of 2 to 4 millions of particles.

Total activity in vial / Total volume in vial	**400 MBq**	**800 MBq**	**1200 MBq**	**1600 MBq**	**2000 MBq**	**2400 MBq**	**2800 MBq**	**3200 MBq**	**3700 MBq**
3 mL	10MBq/ 0.08mL [50,000-100,000]	10MBq/ 0.04mL [25,000-50,000]	10MBq/ 0.026 mL [16,670-33,330]	10MBq/ 0.02 mL [12,500-25,000]	10MBq/ 0.016 mL [10,000-20,000]	10MBq/ 0.015 mL [8,330-16,670]	10MBq/ 0.01 mL [7,140-14,290]	10MBq/ 0.009 mL [6,250-12,500]	10MBq/ 0.008 mL [5,400-10,810]
	40MBq/ 0.3mL [200,000-400,000]	40MBq / 0.15mL [100,000-200,000]	40MBq/ 0.1mL [66,670-133,330]						
		80MBq/ 0.3mL [200,000-400,000]	80MBq/ 0.2mL [133,330-266,670]	80MBq/ 0.16mL [100,000-200,000]	80MBq/ 0.128mL [80,000-160,000]	80MBq/ 0.12 mL 66,670-133,330]			
		110MBq/ 0.45mL [275,000-550,000]	110MBq/ 0.286mL [183,330-366,670]	110MBq/ 0.22 mL [137,500-275,000]	110MBq/ 0.176 mL [110,000-220,000]	110MBq/ 0.165 mL [91,670-183,330]	110MBq/ 0.11 mL [78,570-157,140]	110MBq/ 0.1mL [68,750-137,500]	
			150MBq/ 0.39mL [250,000-500,000]	150MBq/ 0.3mL [187,500-375,000]	150MBq/ 0.24mL [150,000-300,000]	150MBq/ 0.225mL [125,000-250,000]	150MBq/ 0.15mL [107,140-214,290]	150MBq/ 0.135mL [93,750-187,500]	150MBq/ 0.12mL [81,080-162,160]
			185MBq/ 0.48mL [308,330-616,670]	185MBq/ 0.37mL [231,250-462,500]	185MBq/ 0.3mL [185,000-370,000]	185MBq/ 0.27mL [154,170-308,330]	185MBq/ 0.185mL [132,140-264,290]	185MBq/ 0.17mL [115,630-231,250]	185MBq/ 0.15mL [100,000-200,000]
			200MBq/ 0.5mL [333,330-666,670]	200MBq/ 0.38mL [250,000-500,000]	200MBq/ 0.3mL [200,000-400,000]	200MBq/ 0.25mL [166,670-333,330]	200MBq/ 0.21mL [142,860-285,710]	200MBq/ 0.18 mL [125,000-250,000]	200MBq/ 0.16mL [108,110-216,220]
5 mL	10MBq/ 0.125mL [50,000-100,000]	10MBq/ 0.06mL [25,000-50,000]	10MBq/ 0.04mL [16,670-33,330]	10MBq/ 0.03mL [12,500-25,000]	10MBq/ 0.025mL [10,000-20,000]	10MBq/ 0.02mL [8,330-16,670]	10MBq/ 0.018mL [7,140-14,290]	10MBq/ 0.015mL [6,250-12,500]	10MBq/ 0.013mL [5,400-10,810]
	40MBq/ 0.5mL [200,000-400,000]	40MBq/ 0.25mL [100,000-200,000]	40MBq/ 0.17mL [66,670-133,330]						
		80MBq/ 0.5mL [200,000-400,000]	80MBq/ 0.33mL [133,330-266,670]	80MBq/ 0.25mL [100,000-200,000]	80MBq/ 0.2mL [80,000-160,000]	80MBq/ 0.17mL 66,670-133,330]			
		110MBq/ 0.68mL [275,000-550,000]	110MBq/ 0.45mL [183,330-366,670]	110MBq/ 0.34mL [137,500-275,000]	110MBq/ 0.275mL [110,000-220,000]	110MBq/ 0.23mL [91,670-183,330]	110MBq/ 0.19mL [78,570-157,140]	110MBq/ 0.17mL [68,750-137,500]	

			150MBq/ 0.62mL [250,000-500,000]	150MBq/ 0.47mL [187,500-375,000]	150MBq/ 0.375mL [150,000-300,000]	150MBq/ 0.31mL [125,000-250,000]	150MBq/ 0.26mL [107,140-214,290]	150MBq/ 0.23mL [93,750-187,500]	150MBq/ 0.2mL [81,080-162,160]
			185MBq/ 0.77mL [308,330-616,670]	185MBq/ 0.57mL [231,250-462,500]	185MBq/ 0.46mL [185,000-370,000]	185MBq/ 0.38mL [154,170-308,330]	185MBq/ 0.33mL [132,140-264,290]	185MBq/ 0.29mL [115,630-231,250]	185MBq/ 0.25mL [100,000-200,000]
			200MBq/ 0.83mL [333,330-666,670]	200MBq/ 0.62mL [250.000-500.000]	200MBq/ 0.5mL [200,000-400,000]	200MBq/ 0.42mL [166,670-333,330]	200MBq/ 0.36mL [142,860-285,710]	200MBq/ 0.31 mL [125,000-250,000]	200MBq/ 0.27mL [108,110-216,220]

Table 3 (continued)

Total activity in vial / Total volume in vial	400 MBq	800 MBq	1200 MBq	1600 MBq	2000 MBq	2400 MBq	2800 MBq	3200 MBq	3700 MBq
7 mL	10MBq/ 0.175mL [50,000-100,000]	10MBq/ 0.08mL [25,000-50,000]	10MBq/ 0.058mL [16,670-33,330]	10MBq/ 0.04mL [12,500-25,000]	10MBq/ 0.035mL [10,000-20,000]	10MBq/ 0.03mL [8,330-16,670]	10MBq/ 0.025mL [7,140-14,290]	10MBq/ 0.02mL [6,250-12,500]	10MBq/ 0.019mL [5,400-10,810]
	40MBq/ 0.7mL [200,000-400,000]	40MBq/ 0.35mL [100,000-200,000]	40MBq/ 0.23mL [66,670-133,330]						
		80MBq/ 0.7mL [200,000-400,000]	80MBq/ 0.47mL [133,330-266,670]	80MBq/ 0.35mL [100,000-200,000]	80MBq/ 0.28mL [80,000-160,000]	80MBq/ 0.12mL 66,670-133,330]			
		110MBq/ 0.96mL [275,000-550,000]	110MBq/ 0.64mL [183,330-366,670]	110MBq/ 0.48mL [137,500-275,000]	110MBq/ 0.385mL [110,000-220,000]	110MBq/ 0.32mL [91,670-183,330]	110MBq/ 0.275mL [78,570-157,140]	110MBq/ 0.24mL [68,750-137,500]	
			150MBq/ 0.87mL [250,000-500,000]	150MBq/ 0.65mL [187,500-375,000]	150MBq/ 0.525mL [150,000-300,000]	150MBq/ 0.44mL [125,000-250,000]	150MBq/ 0.375mL [107,140-214,290]	150MBq/ 0.33mL [93,750-187,500]	150MBq/ 0.28mL [81,080-162,160]
			185MBq/ 1.08mL [308,330-616,670]	185MBq/ 0.81mL [231,250-462,500]	185MBq/ 0.65mL [185,000-370,000]	185MBq/ 0.54mL [154,170-308,330]	185MBq/ 0.46mL [132,140-264,290]	185MBq/ 0.40mL [115,630-231,250]	185MBq/ 0.35mL [100,000-200,000]
			200MBq/ 1.16mL [333,330-666,670]	200MBq/ 0.87mL [250.000-500.000]	200MBq/ 0.7mL [200,000-400,000]	200MBq/ 0.58mL [166,670-333,330]	200MBq/ 0.5mL [142,860-285,710]	200MBq/ 0.43mL [125,000-250,000]	200MBq/ 0.38mL [108,110-216,220]
10 mL	10MBq/ 0.25mL [50,000-100,000]	10MBq/ 0.125mL [25,000-50,000]	10MBq/ 0.08mL [16,670-33,330]	10MBq/ 0.06mL [12,500-25,000]	10MBq/ 0.05mL [10,000-20,000]	10MBq/ 0.04mL [8,330-16,670]	10MBq/ 0.035mL [7,140-14,290]	10MBq/ 0.03mL [6,250-12,500]	10MBq/ 0.027mL [5,400-10,810]
	40MBq/1 mL [200,000-400,000]	40MBq/0.5mL [100,000-200,000]	40MBq/ 0.33mL [66,670-133,330]						
		80MBq/1 mL [200,000-400,000]	80MBq/ 0.66mL [133,330-266,670]	80MBq/ 0.5mL [100,000-200,000]	80MBq/ 0.4mL [80,000-160,000]	80MBq/ 0.33mL 66,670-133,330]			
		110MBq/ 1.37mL [275,000-550,000]	110MBq/ 0.92mL [183,330-366,670]	110MBq/ 0.68mL [137,500-275,000]	110MBq/ 0.55mL [110,000-220,000]	110MBq/ 0.46mL [91,670-183,330]	110MBq/ 0.39mL [78,570-157,140]	110MBq/ 0.34mL [68,750-137,500]	

		150MBq/ 1.25mL [250,000-500,000]	150MBq/ 0.93mL [187,500-375,000]	150MBq/ 0.75mL [150,000-300,000]	150MBq/ 0.62mL [125,000-250,000]	150MBq/ 0.53mL [107,140-214,290]	150MBq/ 0.46mL [93,750-187,500]	150MBq/ 0.4mL [81,080-162,160]
		185MBq/ 1.54mL [308,330-616,670]	185MBq/ 1.15mL [231,250-462,500]	185MBq/ 0.93mL [185,000-370,000]	185MBq/ 0.77mL [154,170-308,330]	185MBq/ 0.66mL [132,140-264,290]	185MBq/ 0.58mL [115,630-231,250]	185MBq/ 0.5mL [100,000-200,000]
		200MBq/ 1.66mL [333,330-666,670]	200MBq/ 1.25mL [250.000-500.000]	200MBq/ 1mL [200,000-400,000]	200MBq/ 0.83mL [166,670-333,330]	200MBq/ 0.71mL [142,860-285,710]	200MBq/ 0.62mL [125,000-250,000]	200MBq/ 0.54mL [108,110-216,220]

3. It is necessary to calculate the activity taking into account the decrease of (^{99m}Tc) between the time of labelling and the time of injection. The decay table of (^{99m}Tc) is presented in table 4.

Table 4

^{99m}Tc (HALF-LIFE : 6.02 hours) DECAY TABLE

H Min	%	H Min	%	H Min	%	H Min	%	H Min	%	H Min	%
0 05	99.05	2 05	78.67	4 05	62.49	6 05	49.64	8 05	39.43	10 05	31.32
0 10	98.10	2 10	77.92	4 10	61.89	6 10	49.16	8 10	39.05	10 10	31.02
0 15	97.16	2 15	77.18	4 15	61.30	6 15	48.69	8 15	38.68	10 15	30.72
0 20	96.23	2 20	76.44	4 20	60.72	6 20	48.23	8 20	38.61	10 20	30.43
0 25	95.32	2 25	75.71	4 25	60.14	6 25	47.77	8 25	37.94	10 25	30.14
0 30	94.41	2 30	74.99	4 30	59.56	6 30	47.31	8 30	37.58	10 30	29.85
0 35	93.50	2 35	74.27	4 35	58.99	6 35	46.86	8 35	37.22	10 35	29.57
0 40	92.61	2 40	73.56	4 40	58.43	6 40	46.41	8 40	36.87	10 40	29.28
0 45	91.73	2 45	72.86	4 45	57.87	6 45	45.97	8 45	36.51	10 45	29.00
0 50	90.85	2 50	72.16	4 50	57.32	6 50	45.53	8 50	36.17	10 50	28.73
0 55	89.98	2 55	71.47	4 55	56.77	6 55	45.10	8 55	35.82	10 55	28.45
1 00	89.12	3 00	70.79	5 00	56.23	7 00	44.66	9 00	35.48	11 00	28.18
1 05	88.27	3 05	70.12	5 05	55.69	7 05	44.24	9 05	35.14	11 05	27.91
1 10	87.43	3 10	69.45	5 10	55.16	7 10	43.82	9 10	34.80	11 10	27.64
1 15	86.60	3 15	68.78	5 15	54.64	7 15	43.40	9 15	34.47	11 15	27.38
1 20	85.77	3 20	68.13	5 20	54.11	7 20	42.98	9 20	34.14	11 20	27.12
1 25	84.95	3 25	67.48	5 25	53.60	7 25	42.57	9 25	33.82	11 25	26.86
1 30	84.14	3 30	66.83	5 30	53.09	7 30	42.17	9 30	33.49	11 30	26.60
1 35	83.33	3 35	66.19	5 35	52.58	7 35	41.76	9 35	33.17	11 35	26.35
1 40	82.54	3 40	65.56	5 40	52.08	7 40	41.36	9 40	32.86	11 40	26.10
1 45	81.75	3 45	64.94	5 45	51.58	7 45	40.97	9 45	32.54	11 45	25.85
1 50	80.97	3 50	64.32	5 50	51.09	7 50	40.58	9 50	32.23	11 50	25.60
1 55	80.20	3 55	63.70	5 55	50.60	7 55	40.19	9 55	31.92	11 55	25.36
2 00	79.43	4 00	63.09	6 00	50.12	8 00	39.81	10 00	31.62	12 00	25.12

Method of preparation

Usual precautions regarding sterility and radioprotection should be respected.

1. Take a vial from the kit and put it in an appropriate lead shielding.

Using a hypodermic syringe, introduce through the rubber stopper 3 to 10 mL of sterile and pyrogen-free sodium pertechnetate (^{99m}Tc) injection, radioactivity varying as a function of the volume from 400 to maximum 3700 MBq.

Sodium pertechnetate (^{99m}Tc) injection should comply with European Pharmacopoeia specifications.

2. Do not use a breather needle as the content is under nitrogen: after introduction of the volume of sodium pertechnetate (^{99m}Tc) injection, without removing the needle, withdraw an equivalent volume of nitrogen in order to avoid excess pressure in the vial.

Shake for about 2 minutes and wait for 15 minutes before use.

After radiolabelling the technetium (^{99m}Tc) macrosalb suspension obtained is a whitish homogenous suspension which may separate on standing, with a pH range between 5.0 and 7.0.

The vial should be shaken before each withdrawal in order to homogenise the suspension.

The syringe should be swirled immediately prior to injection to homogenise the injectate.

The homogeneity of the prepared suspension, pH, radioactivity and gamma spectrum should be checked before use.

Quality control

The quality of labelling (radiochemical purity) could be checked according to the following procedure:

Method

Non-filterable radioactivity.

Materials and methods

1. Polycarbonate membrane filter 13 mm to 25 mm in diameter, 10 µm thick and with circular pores 3 µm in diameter.
2. 0.9 % sodium chloride solution.
3. Miscellaneous: syringes, needles, 15 mLglass vials, appropriate counting apparatus.

Procedure

1. Fit the membrane into a suitable holder.
2. Place 0.2 mL of the injection on the membrane. Measure the radioactivity of the membrane : Activity 1.
3. Rinse the membrane with 20 mL of sodium chloride 9 mg/mL (0.9 %) solution and collect the filtrate in a vial for elimination.
4. Measure the radioactivity remaining on the membrane: Activity 2.
5. Calculations:

   Calculate the percentage of technetium (^{99m}Tc) human albumin macroaggregates as follows:

$$\frac{\text{Activity 2}}{\text{Activity 1}} \times 100$$

The radioactivity remaining on the membrane should be not less than 90 % of the total radioactivity of the injection.

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 MHRA.