

**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 of macroaggregated human albumin (macroalbu).

The number of particles per vial is ranging between 2 and 4 million. In the labelled product 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 ( $^{99m}\text{Tc}$ ) solution, the suspension of technetium( $^{99m}\text{Tc}$ ) - 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;
- To assess regional relative lung function prior to surgeries that significantly reduce lung perfusion such as (partial) lung resection, to follow-up the lung transplants or to assist in 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.

- Hepato-pulmonary shunt detection before selective internal radiation therapy (SIRT) of primary and secondary liver tumours.

- Radio-guided occult lesion localisation (ROLL) of breast and lungs tumours.

## 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

#### Adult and elderly patients

##### Pulmonary perfusion scintigraphy

The recommended activity intravenously administered to an adult weighing 70 kg is between 40 and 150 MBq, with a mean 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 activities to be administered to children and to adolescents may be calculated according to the recommendation of Paediatric Task Group of the European Association of Nuclear Medicine (EANM 2016) by multiplying a baseline activity by a patient's weight-dependent correction factor (table 1) :

$A[\text{MBq}]_{\text{administered}} = \text{baseline activity} \times \text{correction factor}$

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.

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

Weight [kg]	Factor	Weight [kg]	Factor	Weight [kg]	Factor
<b>3</b>	= 1	<b>22</b>	= 5.29	<b>42</b>	= 9.14
<b>4</b>	= 1.14	<b>24</b>	= 5.71	<b>44</b>	= 9.57
<b>6</b>	= 1.71	<b>26</b>	= 6.14	<b>46</b>	= 10.00
<b>8</b>	= 2.14	<b>28</b>	= 6.43	<b>48</b>	= 10.29
<b>10</b>	= 2.71	<b>30</b>	= 6.86	<b>50</b>	= 10.71
<b>12</b>	= 3.14	<b>32</b>	= 7.29	<b>52-54</b>	= 11.29
<b>14</b>	= 3.57	<b>34</b>	= 7.72	<b>56-58</b>	= 12.00
<b>16</b>	= 4.00	<b>36</b>	= 8.00	<b>60-62</b>	= 12.71
<b>18</b>	= 4.43	<b>38</b>	= 8.43	<b>64-66</b>	= 13.43
<b>20</b>	= 4.86	<b>40</b>	= 8.86	<b>68</b>	= 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 EANM guidelines for lung scintigraphy in children (2007):

<b>Weight [kg]</b>	<b>Maximum number of particles to be administered</b>
<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.

- Hepato-pulmonary shunt detection before selective internal radiation therapy (SIRT)  
The recommended activity administered to an adult weighing 70 kg is 100 MBq.

- Radio-guided occult lesion localisation (ROLL)

In breast tumours, 10 to 20 MBq in 0.2 mL of radiolabelled solution, followed by the administration of 0.2 mL of saline solution to avoid backflow of the radiolabelled product to the injection site.

In lungs tumours, 50 to 110 MBq in 0.2 mL of radiolabelled solution, followed by the administration of 0.2 mL of saline solution to avoid backflow of the radiolabelled product to the injection site.

**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.

- Pulmonary perfusion scintigraphy

The labelled solution must be administered intravenously.

Blood should never be drawn up into the syringe because that induces the formation of small clots responsible for obstruction of larger arterioles, resulting in false positive uptakes (“hot spots”) on the scintigraphic images.

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.

The medicinal product is slowly injected intravenously for at least 30 seconds.

Great care must be taken that the radioactive product does not enter the surrounding tissues and that no blood is aspirated into the syringe, 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.

- Hepato-pulmonary shunt detection before selective internal radiation therapy  
The labelled solution must be administered via a catheter into the hepatic artery.

- Radio-guided occult lesion localisation  
The labelled solution must be administered intratumorally the day before the procedure.

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, 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 a 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 (<sup>99m</sup>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 (<sup>99m</sup>Tc) macrosalb may not be administered except after a careful benefit/risk analysis.

In order to minimize the possibility of microembolism to the cerebral and renal circulations, technetium (<sup>99m</sup>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 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 section 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.

### 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 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 ( $^{99m}\text{Tc}$ ) macrosalb may be induced by different medicinal products.

- Pharmacologic interactions are caused by chemotherapeutic medicinal products, heparin and bronchodilators.

- Toxicologic 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 patient receiving intravenous therapy with magnesium sulphate; 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 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 the foetus.

## **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 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 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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 and chest pain, 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.
- Pneumothorax may occur in case of intratumoral injection in the lungs

## **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.

### **4.9 Overdose**

The number of particles per adult patient must not exceed  $1.5 \times 10^6$ .

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 ( $^{99m}\text{Tc}$ ) macrosalb 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. It might be helpful to estimate the effective dose that was applied.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, technetium (<sup>99m</sup>Tc), particles for injection, ATC code: V09EB01**

At the chemical concentrations used for diagnostic examinations, technetium (<sup>99m</sup>Tc) macrosalb does not appear to have any pharmacodynamic activity.

### 5.2 Pharmacokinetic properties

#### Distribution

Following intravenous injection of technetium (<sup>99m</sup>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 1,000,000<sup>th</sup> capillary (diameter < 20 micrometer) and every 1,000<sup>th</sup> 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 characterized.

### 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.

With particulars from 10 to 50 micrometers in diameter the first pulmonary signs of toxicity in dogs (e.g. tachypnea) appear after injection of 20 to 25 mg per kg of body weight.

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 doses exceed 5 mg/kg.

Doses of 20-50 mg/kg cause sudden death from respiratory failure. A safety factor of 100 is found after injection in dogs of 14,000 particles of technetium (<sup>99m</sup>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 and no significant pathological changes in the main organs.

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**

Stannous chloride dihydrate (E 512)  
Human serum albumin  
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**

12 months.

The expiry date is indicated on the outer packaging and on each vial.

After radiolabelling: 8 hours. Store in a refrigerator (2°C – 8°C).

### **6.4 Special precautions for storage**

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

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

Storage of radiopharmaceuticals should be in accordance with national regulations 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 licenses 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 (<sup>99m</sup>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 extemporaneous preparation is not radioactive. However, after sodium pertechnetate (<sup>99m</sup>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 or 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 AUTHORIZATION HOLDER**

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

## **8      MARKETING AUTHORIZATION NUMBER**

Country specific

## **9      DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION**

Country specific

## **10     DATE OF REVISION OF THE TEXT**

07/2021

## 11. DOSIMETRY

Technetium ( $^{99m}\text{Tc}$ ) is produced by means of a ( $^{99}\text{Mo}/^{99m}\text{Tc}$ ) 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 ( $^{99}\text{Tc}$ ) which, in view of its long half-life of  $2.13 \times 10^5$  years can be regarded as quasi stable.

The data listed below are from ICRP 128 publication for intravenous administration:

Organ	DOSE ABSORBED PER ACTIVITY ADMINISTERED (mGy / MBq)				
	Adult	15 year old	10 year old	5 year old	1 year old
Adrenals	0.0068	0.0088	0.013	0.019	0.031
Bone surfaces	0.0051	0.0063	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	0.0080	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	0.0043	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
<b>Effective dose (mSv/MBq)</b>	<b>0.011</b>	<b>0.016</b>	<b>0.023</b>	<b>0.034</b>	<b>0.063</b>

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 ( $^{99m}\text{Tc}$ ) 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 ( $^{99m}\text{Tc}$ ) 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:

$$\text{Labelling volume} = \frac{\text{Number of macroaggregate particles per vial } (3 \cdot 10^6) \times \text{Volume to inject}}{\text{Number of macroaggregate particles to be injected per dose}}$$

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:

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

Table 3 can be used to calculate the volume and activity of the pertechnetate ( $^{99m}\text{Tc}$ ) solution to be added depending on the activity and the number of macroaggregates per dose.

**Table 3**

Total activity Total volume	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]
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 Total volume	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/1mL [200,000- 400,000]	40MBq/0.5m L [100,000- 200,000]	40MBq/ 0.33mL [66,670- 133,330]							
		80MBq/1mL [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 technetium ( $^{99m}\text{Tc}$ ) between the time of labelling and the time of injection. The decay table of technetium ( $^{99m}\text{Tc}$ ) is presented in table below.

<b><sup>99m</sup>Tc (HALF-LIFE : 6.02 hours) DECAY TABLE</b>																	
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.

Sodium pertechnetate (<sup>99m</sup>Tc) injection should comply with European Pharmacopoeia specifications.

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 (<sup>99m</sup>Tc) injection, radioactivity varying as a function of the volume from 400 MBq to maximum 3700 MBq.

**2. Do not use a breather needle as the contents is under nitrogen:** after introduction of the volume of sodium pertechnetate (<sup>99m</sup>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 (<sup>99m</sup>Tc) macrosalb suspension obtained is a whitish homogenous suspension which may separate on standing, with a pH ranges between 5.0 and 7.0. The homogeneousness of the suspension after preparation, pH, radioactivity and gamma spectrum should be checked before use.

**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.

### **Quality control**

The quality of labeling (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 mL glass 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 (<sup>99m</sup>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.