PULMOCIS®

Kit for the preparation of technetium (^{99m}Tc) human albumin macroaggregates injection

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PULMOCIS
Kit for the preparation of technetium (^{99m}Tc) human albumin macroaggregates injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human albumin as macroaggregates : 2.0 mg/vial

For excipients, see 6.1.

The product contains no antimicrobial preservative.

The macroaggregates number per vial is ranging between 2 and 4 millions.
No macroaggregate has a size higher than 150 µm.
Not more than 10 of them have a size higher than 100µm.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
Powder for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Pulmonary perfusion scintigraphy.

As secondary indication ^{99m}Tc-albumin macroaggregates may be used for venoscintigraphy.

4.2 Posology and method of administration

Recommended activities to be administered intravenously to an adult weighing 70 kg vary between 37 - 185 MBq. The number of particles per administered dose must be in a range of 60×10^3 - 700×10^3.
The lung test may start immediately after injection.
The activity to be administered in children should be a fraction of the adult activity and should be calculated according to the following equation :

$$\text{Pediatric dose (MBq)} = \frac{\text{Adult dose (MBq) x child weight (kg)}}{70 \text{ kg}}$$

Although body weight is the more used factor on which to base the adjustment of the activity administered, in a limited number of cases the body surface area may be considered to be more appropriate.

$$\text{Pediatric dose (MBq)} = \frac{\text{Adult dose (MBq) x child surface (m}^2\text{)}}{1.73}$$

4.3 Contraindications

Hypersensitivity to the active substance(Human albumin as macroaggregates) or to any of the excipients.

4.4 Special warnings and special precautions for use

Radiopharmaceuticals should be used only by authorised persons. Their receipt, use, transfer and disposal are subject to national licensing regulations.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical requirements.

The syringe should be swirled immediately prior to injection to homogenise the injectate. Blood should never be drawn into the syringe because that induces the formation of small clots.

Special care should be exercised when administering ^{99m}Tc-MAA to patients with significant right to left cardiac shunt. In order to minimise the possibility of microembolism to the cerebral and renal circulations ^{99m}Tc-MAA should be given by slow intravenous injection and the number of particles reduced by up to 50%. Such precautions are also advised in patients with respiratory failure complicating pulmonary hypertension.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Changes in the biological distribution of ^{99m}Tc-MAA are induced by differents drugs.

Pharmacologic interactions are caused by chemotherapeutic agents, heparin, bronchodilators.

Toxicologic interactions are caused by heroin, nitrofurantoin, busulfan, cyclophosphamide, bleomycin, methotrexate, methysergide.

Pharmaceutic interactions are caused by magnesium sulphate.

4.6 Pregnancy and lactation

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should always be considered.

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

Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of radioactivity in breast milk. If the administration is considered necessary, breast feeding should be interrupted for 12 hours and the expressed feeds discarded. Breast feeding can be restarted when the radioactivity level in the milk will not result in a radiation dose to the child greater than 1 mSv.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Single or repeated injections of ^{99m}Tc-albumin macroaggregates may be associated with hypersensitive-type reactions, with chest pain, rigor and collapse. Local allergic reactions have been seen at the injection site.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggest that these adverse effects will occur with low frequency because of the low radiation doses incurred.

For most diagnostic investigation using a nuclear medicine procedure the radiation dose delivered (E) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

Overdose, as commonly intended (i.e., excessive quantity in weight) is not expected, but overdose may be understood as the administration of a very high number of particles. The number of MAA particles per adult patient must not exceed 1.5×10^6.

The dangers to be expected relating to the inadvertent administration of excess radioactivity may be reduced by promoting a diuresis and frequent voiding of urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Radiopharmaceutical preparation for diagnostic use.
ATC code: V09EB02

^{99m}Tc-MAA, when administered in usual doses, show no pharmacodynamic effects detectable clinically and/or analytically.

5.2 Pharmacokinetic properties

Following injection into a superficial vein of the systemic venous circulation, the macroaggregates are carried at the speed of this circulation to the first capillary filter, i.e. the capillary tree of the pulmonary artery system. 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. When pulmonary flow distribution is normal, the compound distributes over the entire pulmonary area following physiologic gradients; when district flow is altered the areas of reduced flow are reached by a proportionally smaller amount of particles. The technetium labeled macroaggregates remain in the lungs for variable periods of time, depending of the structure, size and number of particles.

The disappearance of activity from the particles in the lungs is governed by an exponential law: the larger aggregate have a longer biological half-life, whereas particles between 5 and 90 µm in diameter have a half-life ranging from 2 to 8 hours.

The decrease in pulmonary concentration is caused by the mechanical break-down of the particles occluding the capillaries, stemming from the systo-diastolic pressure pulsations within the capillary itself.

The products of macroaggregate break-down, once recirculated as albumin microcolloid, are quickly removed by the macrophages of the reticuloendothelial system, i.e. essentially the liver and the spleen.

The microcolloid is metabolised with introduction of the radioactive label (^{99m}Tc) into the systemic circulation from which it is removed and excreted in urine.

5.3 Preclinical safety data

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

The pathophysiologic mechanism responsible for toxicity is shown to be the increase of the pulmonary blood pressure. With particles from 10 to 50 µm 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 µm sized MAA are injected, where no significant pressure changes are recorded with 40 mg of less than 35 µm MAA particles.
With suspension of MAA up to 150 µm diameter, no blood pressure changes appear below 10 mg/kg, while larger diameter suspensions (up to 300 µm) typical blood pressure changes in pulmonary artery appear when the dose exceeds 5 mg/kg.

Doses of 20-50 mg/kg cause sudden death for respiratory failure. A safety factor of 100 is found after injection in dogs of 14 000 ^{99m}Tc-MAA (size : 30-50 µm).

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 unlabeled product.

5.4 Radiation dosimetry

Technetium (^{99m}Tc) decays with the emission of gamma radiation with energy of 140 keV and a half life of 6 hours to technetium (^{99}Tc) which can be regarded as quasi stable.
For this product the effective dose resulting from an administered activity of 185 MBq is typically 2.0 mSv (per 70 kg individual).

According to ICRP 80 (1998) the radiation doses absorbed by the patients are the following:

	ABSORBED DOSE PER UNIT ADMINISTERED (mGy / MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	6.8E-03	8.8E-03	1.3E-02	1.9E-02	3.1E-02
Bladder	8.7E-03	1.1E-02	1.4E-02	1.6E-02	3.0E-02
Bone surfaces	5.1E-03	6.4E-03	9.1E-03	1.4E-02	2.6E-02
Brain	9.2E-04	1.2E-03	2.0E-03	3.2E-03	5.5E-03
Breast	5.0E-03	5.6E-03	9.9E-03	1.4E-02	2.1E-02
Gall bladder	5.6E-03	7.0E-03	1.0E-02	1.6E-02	2.4E-02
GI-tract					
Stomach	3.7E-03	5.2E-03	8.0E-03	1.2E-02	2.0E-02
SI	2.0E-03	2.6E-03	4.3E-03	6.8E-03	1.2E-02
Colon	1.9E-03	2.6E-03	4.3E-03	6.9E-03	1.2E-02
(ULI	2.2E-03	2.9E-03	5.0E-03	8.3E-03	1.4E-02
(LLI	1.6E-03	2.1E-03	3.3E-03	5.0E-03	9.5E-03
Heart	9.6E-03	1.3E-02	1.8E-02	2.5E-02	3.8E-02
Kidneys	3.7E-03	4.8E-03	7.2E-03	1.1E-02	1.8E-02
Liver	1.6E-02	2.1E-02	3.0E-02	4.2E-02	7.4E-02
Lungs	6.6E-02	9.7E-02	1.3E-01	2.0E-01	3.9E-01
Muscles	2.8E-03	3.7E-03	5.2E-03	7.7E-03	1.4E-02
Oesophagus	6.1E-03	7.7E-03	1.1E-02	1.5E-02	2.2E-02
Ovaries	1.8E-03	2.3E-03	3.5E-03	5.4E-03	1.0E-02
Pancreas	5.6E-03	7.5E-03	1.1E-02	1.7E-02	2.9E-02
Red marrow	3.2E-03	3.8E-03	5.3E-03	7.2E-03	1.2E-02
Skin	1.5E-03	1.7E-03	2.7E-03	4.3E-03	7.8E-03
Spleen	4.1E-03	5.5E-03	8.3E-03	1.3E-02	2.2E-02
Testes	1.1E-03	1.4E-03	2.2E-03	3.3E-03	6.2E-03
Thymus	6.1E-03	7.7E-03	1.1E-02	1.5E-02	2.2E-02
Thyroid	2.5E-03	3.3E-03	5.7E-03	9.0E-03	1.6E-02
Uterus	2.2E-03	2.8E-03	4.2E-03	6.0E-03	1.1E-02
Remaining organs	2.8E-03	3.6E-03	5.0E-03	7.4E-03	1.3E-02
Effective dose (mSv/MBq)	**1.1E-02**	**1.6E-02**	**2.3E-02**	**3.4E-02**	**6.3E-02**

For an administered activity of 185 MBq the typical radiation dose to the target organ, lungs, is 12.21 mGy and the typical radiation dose to the critical organs, adrenals, bladder, liver, pancreas, spleen, are 1.26, 2.03, 2.96, 1.04 and 0.76 mGy respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Stannous chloride dihydrate
Sodium chloride
Under nitrogen atmosphere

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

12 months.
The expiry date is indicated on the outer packaging and on each vial.
The labeled product should be used within 8 hours after labeling.

6.4 Special precautions for storage

Store the kit and the labeled product at 2°C – 8°C (in a refrigerator).
Storage should be in accordance with national regulations for 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: kit of 5 multidose vials.

6.6 Instructions for use, handling, and disposal

Pulmocis is a kit for the preparation of technetium (^{99m}Tc) human albumin macroaggregates injection, ((^{99m}Tc)-MAA), containing a sterile, pyrogen-free, freeze-dried product under nitrogen.

The product is to be used after labeling by the addition of sterile, pyrogen free isotonic sodium pertechnetate (^{99m}Tc) injection, allowing the preparation of Technetium (^{99m}Tc) human albumin macroaggregates injection.

Method of preparation

Usual precautions regarding sterility and radioprotection should be respected.

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

Using a hypodermic syringe, introduce through the rubber stopper 2.5 to 10 ml of sterile and pyrogen-free sodium pertechnetate (^{99m}Tc) injection, radioactivity varying as a function of the volume from 92.5 to maximum 3700 MBq.

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

Do not use a breather needle as the contents 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.

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

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

The homogeneousness of the suspension after preparation, pH, radioactivity and gamma spectrum should be checked before use.

The vial should never be opened and must be kept inside its lead shielding. The suspension should be removed aseptically through the stopper with a sterile lead protected syringe.

Determination of volume and activity of pertechnetate in relation with the number of MAA particles per dose.

In order to take into account the number of MAA particles per dose in the determination of volume and radioactivity of pertechnetate to prepare the radiopharmaceutical, charts have been performed and are described hereafter.

The proposed figures in the following tables are calculated from a mean value of 3 millions of MAA particles per vial.

- The first step allows to determine the volume of labeling of the vial as a function of the volume and the number of MAA particles to inject per dose. The used formula is as follows :

$$\textbf{Volume of labeling} = \frac{\text{Number of MAA particles per vial} \times \text{Volume to inject}}{\text{Number of MAA particles to inject per dose}}$$

The tables 1 and 2 show examples for volumes to inject of 0.5, 0.8 and 1 ml.

- The second step allows to know the radioactivity to add in the vial for the labeling as a function of the radioactivity to inject and the previously set parameters. The used formula is as follows :

$$\text{Total radioactivity of the vial} = \frac{\text{Radioactivity to inject} \times \text{Volume of labelling}}{\text{Volume to inject}}$$

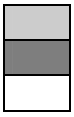
The total radioactivity of the vial is calculated for radioactivities to inject of 37, 74, 111 and 148 MBq. See tables 3,4,5 and 6.

- The third step will describe the decrease calculation taking into account the time of labeling and the time of injection. The decay table of (^{99m}Tc) is presented in table 7.

TABLE 1

DETERMINATION OF THE LABELING VOLUME FROM VOLUME AND NUMBER OF MAA PARTICLES TO INJECT AND CONSIDERING A VIAL CONTAINING 3 MILLIONS MAA PARTICLES

NUMBER OF MAA PARTICLES TO INJECT PER DOSE	VOLUME TO INJECT (mL)		
	0.5	0.8	1
600 000	2.5	4	5
500 000	3	4.8	6
480 000	3.1	5	6.3
428 000	3.5	5.6	7
400 000	3.75	6	7.5
375 000	4	6.4	8
343 000	4.4	7	8.7
330 000	4.5	7.3	9
300 000	5	8	10
267 000	5.6	9	
250 000	6	9.6	
240 000	6.25	10	
215 000	7		
188 000	8		
167 000	9		
150 000	10		



Labeling volume (mL)
Injected volume (mL)
Number of MAA particles to inject / dose

TABLE 2

DETERMINATION OF THE NUMBER OF INJECTED MAA PARTICLES AS A FUNCTION OF THE LABELING VOLUME OF THE VIAL AND THE VOLUME TO INJECT AND CONSIDERING A VIAL CONTAINING 3 MILLIONS MAA PARTICLES

VOLUME OF LABELING (ml)	VOLUME TO INJECT (mL)		
	0.5	0.8	1
3	500 000		
4	375 000	600 000	
5	300 000	480 000	600 000
6	250 000	400 000	500 000
7	215 000	343 000	428 000
8	188 000	300 000	375 000
9	167 000	267 000	330 000
10	150 000	240 000	300 000

Labeling volume (mL)

Injected volume (mL)

Number of MAA particles to inject/dose

TABLES 3, 4, 5 and 6

DETERMINATION OF THE RADIOACTIVITY TO ADD TO THE VIAL AS A FUNCTION OF THE LABELING VOLUME, THE VOLUME AND THE RADIOACTIVITY TO INJECT AND CONSIDERING A VIAL CONTAINING 3 MILLIONS MAA PARTICLES

	37 MBq			74 MBq		
	0.5	**0.8**	**1**	**0.5**	**0.8**	**1**
3	222	139	111	444		
4	296	185	148	592	370	
5	370	231	185	740	462	370
6	444	277	222	888	555	444
7	518	324	259	1036	647	518
8	592	370	296	1184	740	592
9	666	416	333	1332	832	666
10	740	462	370	1480	925	740

Table 3 **Table 4**

	111 MBq			148 MBq		
	0.5	**0.8**	**1**	**0.5**	**0.8**	**1**
3	666			888		
4	888	555		1184	740	
5	1110	694	555	1480	925	740
6	1332	832	666	1776	1110	888
7	1554	980	777	2072	1295	1036
8	1776	1110	888	2368	1480	1184
9	1998	1249	999	2664	1665	1332
10	2220	1387	1110	2960	1850	1480

Table 5 **Table 6**

Injected activity (MBq) **Injected volume (mL)**

Total activity (MBq) **Labeling volume (mL)**

TABLE 7

^{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

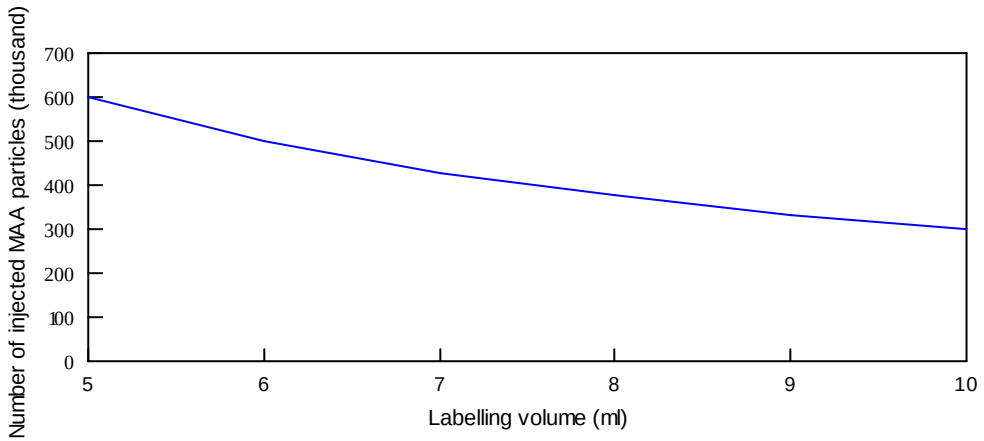
EXAMPLE FOR AN INJECTED VOLUME OF 1 mL

The following table and curve allow to determine the number of MAA particles injected when volumes of labeling are 5 to 10 mL and when the volume to inject is 1 mL.

The proposed figures in the following tables are calculated from a mean value of 3 millions of MAA particles per vial.
The formula used is :

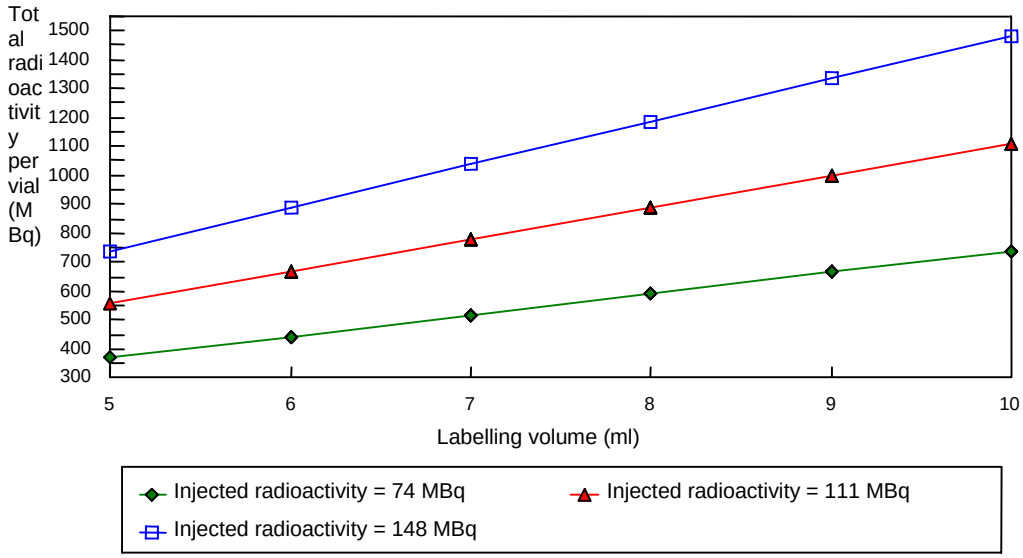
$$\text{Number of injected MAA particles} = \frac{\text{Total number of MAA particles} \times \text{Injected volume}}{\text{Labeling volume}}$$

Volume of labeling (mL)	Number of injected MAA particles
5	600 000
6	500 000
7	428 600
8	375 000
9	333 300
10	300 000



The following table and graph allow to deduce **the total radioactivity to add to the vial** when the radioactivities to inject are 74, 111 or 148 MBq with a injected volume of 1 mL and considering a vial containing 3 millions particles.

Volume of labeling (mL)	Total radioactivity per vial (MBq) with a radioactivity to inject of		
	74 MBq	111 MBq	148 MBq
5	370	555	740
6	444	666	888
7	518	777	1036
8	592	888	1184
9	666	999	1332
10	740	1110	1480



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 assembly.

Procedure

1. Fit the membrane into a suitable holder.
2. Place 1 ml of the injection on the membrane, filter and collect in a vial (A).
3. Rinse the membrane with 2 ml of 0.9% sodium chloride solution and collect in the vial (A).
4. Measure the radioactivity of the filter (X) and the radioactivity of the vial A (Y), using an appropriate detection apparatus.
5. Calculations :

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

$$\frac{X}{X + Y} \times 100$$

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

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.

The residues may be put in a ordinary waste bin insofar as the activity of vials and syringes does not exceed that of background when measured with a low level radiation detector.
Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURER

CIS bio international
BP 32
91192 GIF SUR YVETTE Cedex- FRANCE

COUNTRY	MARKETING AUTHORISATION HOLDER	DISTRIBUTOR
FINLAND	CIS bio international BP 32 91192 GIF SUR YVETTE Cedex-FRANCE MA nr 11244 dated November 1993	Electra-Box Pharma Oy Ojamonharjuntie 21 08100 Lohja FINLAND Tel: +358-193 123 73
SWEDEN	CIS bio international BP 32 91192 GIF SUR YVETTE Cedex-FRANCE MA nr 12906 dated November 1996	Electra-Box Pharma AB PO BOX 2035 – Solkraftsvagen 18B S-135 02 TYRESÖ SWEDEN Tel : +46 (0)8 71 23 000
GREECE	CIS bio international BP 32 91192 GIF SUR YVETTE Cedex-France MA nr 52636 / 3-8-07	AENORASIS 27 Kallergi Street 15127 Melissia, Athens GREECE Tel. : +30.210.613.63.32

7. DATE OF REVISION OF TEXT

08/2008