1. NAME OF THE MEDICINAL PRODUCT

Makro-Albumon 2 mg powder for suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Human Serum Albumin Macroaggregate: 2.0 mg per injection vial
The particle size distribution in the medicinal product is the following: 90% are between 10 and 100 µm, and less than 0.2% of the particles are between 100 and 150 µm. The vial does not contain macroaggregated particle greater than 150 µm.

The particle number per vial is ranging between 2-4x10^6.
The product is prepared from batches of human albumin that has been screened for hepatitis B surface antigen (HbsAg), antibodies for human immunodeficiency virus (anti-HIV) and antibodies for hepatitis C virus (anti-HCV).

Technetium (^{99m}Tc) radionuclide is not part of the kit.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for injection. Kit for radiopharmaceutical preparation.
The medicinal product is sterile, pyrogen free white lyophilised powder seeled under nitrogen atmosphere, to be labelled with sterile sodium (^{99m}Tc) pertechnetate solution in one step.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
After reconstitution and labelling with sodium (^{99m}Tc) pertechnetate solution, the diagnostic agent may be used in the following indications:

- Pulmonary perfusion scintigraphy
  - Pulmonary embolism and myocardial infarct
  - Chronic circulatory failure
  - Local respiratory distress
  - Emphysema
  - Tumour
  - Inflammation
- Visualisation of venous circulation
  - Perfusion arterial scintigraphy of abdominal and retroperitoneal organs
  - Detection of deep vein thrombosis in the lower extremities and pelvis
  - Occlusion of the vena cava inferior

4.2 Posology and method of administration

Posology
Dosage for adults
Recommended activities to be administered intravenously to an adult weighing 70 kg vary between 37 - 185 MBq. Other activities may be justifiable.
The number of particles per administered dose must be in a range of 60 x 10^3 and 700 x 10^3.
The test may start immediately after injection.

Paediatric doses
The activity for children may be calculated from the recommended range of adult activity and adjusted according to body weight. The Paediatric Task Group of EANM recommends calculating the administered activity from the body weight according to the following table.

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

The minimum recommended activity is 15 MBq in case of children under 1 year.
Based on the EANM guideline the recommended particle number to be injected are the following:

Body weight	Particle number
<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

Method of administration
Method of administration: for intravenous use.
This medicinal product should be reconstituted with sodium (^{99m}Tc) pertechnetate solution before administration to the patient.
For instructions on reconstitution and labelling of the medicinal product before administration, see section 6.6 and 12.

Test, image acquisition:
The lung test with gamma camera or SPECT may start immediately after intravenous injection of ^{99m}Tc-Makro-Albumon

4.3 Contraindications

The preparation must not be used for coronarography as coronary artery injections and must not be used for cerebral perfusion scintigraphy studies after injection to artery carotis interna. The preparation must not be given to protein sensitive patients.
Hypersensitivity to the active substance or to any of the excipients listed in point 6.1.

4.4 Special warnings and precautions for use

It should be considered that hypersensitivity (including life-threatening anaphylactic reactions) may occur, therefore advanced resuscitation kit e.g endotracheal tube and ventilator must be immediately available.

Individual risk/benefit justification
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.

General warnings
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 information.
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisation.
Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.
During labelling and use the compliance with radiation protection regulation is mandatory.

Special warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free', this value can be higher after reconstitution with sodium (^{99m}Tc) pertechnetate solution which should be taken into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Lactation
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.

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

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 and symptoms
Frequency not known: hypersensitivity reactions including life-threatening anaphylactoid reactions, chest pain, rigor and collapse may occur.
A hypersensitivity reaction may also occur at the injection site.
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 (EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

The number of MAA particles per adult patient must not exceed 1.5 x 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

Therapeutic indication: Radiopharmaceutical for use in the diagnostic of respiratory system
ATC code: V09E B01
^{99m}Tc-MAA, when administered in usual doses, show no pharmacodynamic effects detectable clinically and/or analytically.

5.2 Pharmacokinetic properties

Distribution
After 5-10 minutes of intravenous injection of ^{99m}Tc-MAKRO-ALBUMON, more than 80% of the albumin aggregated is trapped in the pulmonary alveolar capillary bed causing micro embolism.
Assuming that a sufficient number of radioactive particles has been used, the distribution of radioactive aggregated particles in the normally perfused lung is uniform throughout the vascular bed, and will produce a uniform image. Areas of reduced perfusion will be revealed by a corresponding decreased accumulation of the radioactive particles. The technetium labelled macroaggregates remains in the lungs for variable periods of time, depending of the structure, size and number of particles.

The particle size is ranging between 10 µm and 100 µm. The microembolization caused by the 300,000 to 500,000 particles does not cause detectable circulatory disorders.

Elimination

The radioactivity in the lungs decreases exponentially. The disappearance of activity from the particles in the lungs is governed by a 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

No evidence of pathological changes in the main organs has been detected during the preclinical studies. There is no evidence in the literature of teratogenic, mutagenic or carcinogenic effect of the unlabelled product. 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. tachypnoea) appear after injection of 20 to 25 mg per kg of body weight.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous(II) chloride dihydrate, Sodium chloride, Glucose, Ascorbic acid

6.2 Incompatibilities

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

6.3 Shelf life

18 months

The labelled product should be used within 8 hours after labelling.

6.4 Special precautions for storage

Store in a refrigerator (2 °C -8 °C).

Keep in the original packaging in order to protect from light.

The labelled product should be stored below 25ºC. The labelled product should be used within 8 hours after labelling.

Labelling and handling should be in accordance with national regulations for radioactive materials.

6.5 Nature and contents of container

8 ml, Type I Ph. Eur., colourless glass vials, closed with chlorobutyl rubber stoppers and yellow plastic-aluminium flip off caps.

Each kit contains 6 vials

6.6 Special precautions for disposal

Its receipt, storage, use, transfer and disposal are subject to the regulations and / or appropriate licences of the local competent official organisations.

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

Note: ✠✠ (two crosses)

Classification: **Group II / 3**

In accordance with CLIV 1997 on Health Care, (I), which is applicable under the conditions provided by providers of outpatient care or inpatient services provided by the outpatient clinic under section 3 (g) of the Act.

7. MARKETING AUTHORISATION HOLDER

Medi-Radiopharma Kft.
2030, Érd, Hungary
Szamos út 10-12.
Tel: 06-23-521-261
Fax: 06-23-521-260
e-mail: mediradiopharma-kft@mediradiopharma.hu

8. MARKETING AUTHORISATION NUMBER(S)

OGYI-T-8663/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation:1985. April 30.
Date of the renewal of the authorisation: 2013. August 7.

10. DATE OF REVISION OF THE TEXT

2013. August 7.

11. 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.

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

Absorbed radiation dose (mGy/MBq)					
Organs	**Adult**	**Child**			
		15 yrs	**10 yrs**	**5 yrs**	**1 yr**
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
Remains 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**

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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

Method of preparation

- For labelling use ^{99}Mo/^{99m}Tc generator eluate
- Eluate: the radioactive ^{99m}Tc used for labelling is prepared by eluting the ^{99}Mo-^{99m}Tc generator with physiological NaCl solution.
- If necessary, the eluate may be diluted with a 0.9% sodium chloride solution to obtain the desired activity.
- Take a vial from the kit and put it in an appropriate lead shielding of 3 mm. Using a syringe, introduce through the rubber stopper 2 to 8 ml of sterile and pyrogen-free sodium pertechnetate [^{99m}Tc] injection. Maximum 3700 MBq can be applied. Do not use a breather needle. Without removing the needle, withdraw an equivalent volume of nitrogen in order to avoid excess pressure in the vial. Shake the vial to reconstitute the content. Leave it at 20-25 °C for 20 minutes while swirled the vial occasionally.
- Measure the activity.

The labelled product should be used within 8 hours after labelling.

Radiochemical purity

Method 1: Ascending thin layer chromatography

Materials and methods

1. 2.0 x 20 cm thin layer (Kieselgel 60 DC-Alufolien)
2. Eluent: Acetone
3. Chromatographic jar
4. Syringe, needle, scissors, tweezer, suitable equipment to measure radioactivity

Procedure

1. Pour from the eluent to the jar to have 2 cm deep eluent.
2. Drop from the sample and from 99mTc pertechentate reference solution small quantity (5-10 µl) onto the layer (2 cm from the bottom), dry the layer and place vertically in the jar and cover it. The thin layer should be placed in such a way that the sample drops are over the eluent level.
3. After development, take the thin layer out of the jar, dry and then measure the distribution of the activity by appropriate device.
4. After development in acetone, the labelled material remains at the start point (R_f=0.0), meanwhile the free pertechnetate is on the eluent front (R_f=0.9-1.0).
5. After measuring the activities, determine the percentage of the labelled material and the percentage of the free pertechnetate compared to the total radioactivity.

Determination of labelling efficiency

$$^{99m}\text{Tc-MAKRO-ALBUMON (\%)} = \frac{\text{Radioactivity (cpm) at } R_f = 0.0}{\text{Thin layer total radioactivity (cpm)}} \times 100$$

Determination of radiochemical impurities:

$$\text{Radiochemical impurities (\%)} = \frac{\text{Activity values (cpm) } R_f = 1.0\text{-nél}}{\text{Thin layer total radioactivity (cpm)}} \times 100$$

6. The labelling efficiency should be not less than 90% and the radiochemical impurities should be not more than 10%.

Method 2. Non filtered radioactivity

Use polycarbonate membrane filter of 3 µm pore size fit in a suitable holder.

Place 0.2 ml of the injection on the membrane, rinse the membrane with 20 ml physiological sodium chloride solution Measure the radioactivity of the filter and the radioactivity of the filtrate, using an appropriate device.

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

The residues may be put in an 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. Waste must be disposed of according to national regulations.