TECHNICAL LEAFLET

NAME OF THE MEDICINAL PRODUCT

MAKRO-ALBUMON

1 vial contains 2 mg Human Serum Albumine Macroaggregate
Liophilized powder

QUALITATIVE AND QUANTITATIVE COMPOSITION

Name of the active substance:

Human Serum Albumine Macroaggregate	2.0 mg

Excipient(s):

Stannous(II) Chloride Dihydrate	0.2 mg
Ascorbic Acid	5.0 mg
Glucose	20.0 mg
Sodium Chloride	4.5 mg

PHARMACEUTICAL FORM

The kit is a lyophilised sterile and non-pyrogenic preparation sealed in nitrogen atmosphere, when labelled Technetium-99m-pertechnetate it is suitable for intravenous injection.

1 vial contains 2-4x10^6 particles, the size is mainly in range 10-90 µm. When a suspension of labelled particles is injected intravenously, the majority of particles are removed from the circulation on the first pass through pulmonary capillary bed, permitting pulmonary scintigraphy. The labelled material it is suitable for radionuclide venography of the lower leg or pelvis. The kit 6 vials, 6 self stick-on labels for the indication of the parameters of the labelled preparation and an instruction for use.

CLINICAL PARTICULARS

Therapeutic indications

After labelling with sterile ^{99m}Tc pertechnetate, the kit is suitable for investigations as follows:

- Perfusion lung 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

Posology and method of administration

- Adults, neonates, children and the elderly and mention of the posology for each age category
- Dosage (dose and interval) and duration
- Dosage adjustment in renal or liver insufficiency, dialysis
- Maximum tolerated daily dose and the maximum dose for an entire course of therapy
- Monitoring advice

^{99m}Tc-MAA can use only as intravenous bolus injection. One vial MAKRO-ALBUMON contains particles for 5-6 examinations. Therefore it is very important to pay attention that the whole content of one vial can give never for one patient and also can give never unlabelled aggregated human serum albumin. Before administration must draw there and back to vial the labelled MAKRO-ALBUMON to get homogenous solution. During this must avoid the form of foam.

Dosage for adult

The dosage of lung scintigraphy for adult is 37-185 MBq ^{99m}Tc-MAKRO-ALBUMON and must add intravenously into Vena cubitalis. The injection must apply by resting good and strong breathed patient. Routinely carry out the lung scintigraphy in planar projection: anterior, posterior, right lateral, left lateral, right oblique (30°, 70°) and left oblique (30°, 70°) position.

The minimal particle number for lung perfusion scintigraphy is 50000 particles, the optimal quantity is 100-150000 particle and 500000 particle is the maximum quantity for a diagnostically adequate and free from risk examination is suggested.

Dosage for children

The suggested dose for children must calculate according its body weight and body surface as the portion of dosage for adult:

$$\text{Dose for children} = \frac{\text{Dose of adult (MBq) x body weight of child (kg)}}{\text{70 (kg)}}$$

$$\text{Dose for children} = \frac{\text{Dose of adult (MBq) x body surface of child (m}^2\text{)}}{\text{1,73 (m}^2\text{)}}$$

The suggested quantity of aggregated particle for one year old child is 165 000 particle and must be no more than 50 000 particle for baby. The imaging must carry out immediately in all case after the injection. Usually ^{99m}Tc-MAKRO-ALBUMON is applied to patient only one time, but sometime can repeat it without any allergic reaction. The repeated injection can give in earlier time 36-48 hours after the first injection (accordingly 6-8 halftime of ^{99m}Tc).

Contraindications

- Proved allergic reactions against the native or aggregated human
- serum albumin described also in anamneses.
- Hemodynamic effect, right-left shunt
- Serious pulmonale hypertonie
- Status asthmaticus
- Pregnancy

Special warnings and precautions for use

The preparation containing ^{99m}Tc should not be administered to a person with a history of hypersensitive reactions to human serum albumin. It should not be administered to pregnant women or lactating mothers or those less than 18 years of age except when the value of the desired clinical information exceeds the risk of the radiation burden incurred by the patient. With women of childbearing potential, the investigation should be performed during the first 10 days after the onset of menses. The labelled molecule can be used within 8 hours after reconstitution. The suspension is always to be shaken by injecting it into and withdrawing it from the vial. The labelled preparation can be diluted, if needed, by the addition of sterile, isotonic saline. The labelled preparation is to be kept in below 25 °C and protected from oxidants.

Both the labelling and the clinical utilisation of this product should be carried out in a manner that satisfies radiological safety and pharmaceutical requirements.

The preparation should not be administered to patients without labelling with ^{99m}Tc.

In the event of lung perfusion, the number of labelled particles injected should not exceed 600 000.

Interaction with other medicinal products and other forms of interaction

The biological distribution of ^{99m}Tc-MAKRO-ALBUMON may be modified by some drugs. Heparin, chemotherapeutic agents, heroin, busulfan, nitrofurantoin, cyclophosphamide or bronchodilatators may alter the original biological distribution

Pregnancy and lactation

Investigations of women of child-bearing potential

When it is necessary to administer this radioactive pharmaceutical to a woman of child-bearing potential, information concerning pregnancy should always be sought. Any woman who has missed a period should be assumed to be pregnant until proved otherwise. Where uncertainty exists, it is important that the radiation exposure should be the minimum consistent with attainment of the desired clinical information. Alternative techniques, which do not involve ionising radiation, should also be considered.

Pregnancy

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

Lactation

Before administration of a radiopharmaceutical 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 activity in breast milk. If administration is considered necessary, the breast-feeding should be interrupted for 12 hours and the expressed feeds discarded. Breast- feeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv.

Effects on ability to drive and use machines

MAKRO-ALBUMON no effects on the ability to drive or to operate machines are expected after use of this radioactive medicinal product.

Undesirable effects

If a protein-containing radiopharmaceutical such as ^{99m}Tc-MAKRO-ALBUMON is administered to a patient, hypersensitivity reactions may develop. Adequate medication and reanimation equipment must therefore always be kept available during the investigation. For all patients, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered should be such that the resulting radiation dose is as low as reasonably achievable, bearing in mind the need to obtain the intended diagnostic result.

Overdose

Experiments with MAKRO-ALBUMON on animals indicate that there is no risk of an overdosage.

Overdosage in the classical sense of the word (e.g. intake of an excess amount of the preparation per body weight) does not occur, but for ^{99m}Tc-MAKRO-ALBUMON an overdosage is to be interpreted as an injection of an extremely high number of particles. With adults, the maximum number of particles injected should not exceed 1.5x10^6. The risk of an inadvertent overdosage associated with an intake of surplus radioactivity can be reduced by supportive diuresis, i.e. frequent urination.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ATC code : V09DB01

^{99m}Tc-Makro-Albumon when administered in usual doses and by the usual way, has no pharmacodinamic effect detectable clinically.

Pharmacokinetic properties

At 5-10 minutes after the intravenous injection of ^{99m}Tc-MAKRO-ALBUMON, >80% of the labelled macroaggregates causing microembolism are blocked in the pulmonary capillaries. Their sizes lie in the range 10-90 µm. The microembolism caused by the recommended number of aggregated albumin particles to be administered per dose (3-5x10^5) is so slight that it does not induce any disorder in the pulmonary circulation.

The effective half-life of the macroaggregates in the lung is approximately 3-5 hours, while their biological half-life is about 3-15 hours. During this time, they are fragmented to smaller particles and phagocytosed by the cells of the reticuloendothelial system.

After the intravenous injection, particles measuring <1-10 µm i.e. smaller than the pulmonary capillaries, pass directly to the organs of the reticuloendothelial system (the liver, spleen and bone marrow) and are excreted through the kidneys.

Preclinical safety data

Pathological investigations during preclinical studies did not reveal any pathological lesions in the organs of the laboratory animals. Mutagenicity, teratogenicity or carcinogenicity of the product has not been reported in the relevant literature so far.

PHARMACEUTICAL PARTICULARS

List of excipients

Stannous(II) Chloride Dihydrate
Ascorbic Acid
Glucose
Sodium chloride

Incompatibilities
Not applicable.
Shelf life
The expiry date for the kit is 18 months.
The labelled product should be used within 8 hours after reconstitution with sodium ^{99m}Tc-pertechnetate injection.
Sodium pertechnetate [^{99m}Tc] injection should comply with European Pharmacopoeia specification.
Special precautions for storage
The kit should be stored below 25 °C-in the dark.
Do not store the labelled product above + 25 °C.
Storage should be in accordance with national regulations for radioactive materials.
The contents of the vial are intended only for use in the preparation of radioactive ^{99m}Tc-technetium labelled injection, using the procedure described in user package leaflet.
Radiopharmaceutical should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to licence the use of radionuclides.
Nature and contents of container
In accordance with the requirements of Current European Pharmacopoeia , this is a Type I sterile and transparent glass vial with a capacity of 8 ml closed with sterile rubber stopper and plastic-aluminium caps with turned up edge.
Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements for radioactive materials.
MARKETING AUTHORISATION HOLDER
MEDI-RADIOPHARMA LTD.
2030, Érd Szamos st. 10-12. Hungary
Tel: 36-23-521-261 Fax: 36-23-521-260
e-mail: mediradiopharma-ltd@t-online.hu
MARKETING AUTHORISATION NUMBER(S)
Hungary: OGYI-T-8663-01
Czech Republic: 88/177/91-C
Slovak Republic 88/0120/02-S
Romania 3476/2003/01
Republic of Turkey RF 04-0007
DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Hungary: 30. April 1985/31. January, 2008
Czech Republic: 04. March 1994/13. September 2006
Slovakian Republic: 23. January 2001/16. June 2005
Romania: 04. June 2003
Turkey: 07. July 2004

DATE OF REVISION OF THE TEXT
November, 2007
DOSIMETRY
Radiation burden for adults and children
Estimated Absorbed Radiation Dose after administration of ^{99m}Tc-MAKRO-ALBUMON

Absorbed radiation dose						
Organs	Adult µGy/MBq	Child				Newborn µGy/MBq
		15 yrs µGy/MBq	10 yrs µGy/MBq	5 yrs µGy/MBq	1 yr µGy/MBq	
Lung	70.8	104	145	220	420	1120
Bladder wall	37.1	46.9	68.2	102	186	446
Cardiac wall	9.24	12.2	16.9	23.6	35.8	69.6
Liver	8.24	10.9	15.3	21.6	38.0	77.5
Thymus	6.06	7.61	10.8	14.6	21.2	39.0
Adrenals	5.67	7.47	11.0	16.4	27.5	59.1
Breast	4.91	5.43	9.76	13.8	20.5	39.3
Uterus	4.88	5.93	9.18	13.4	23.2	43.5
Bone surface	4.73	5.98	8.51	12.9	24.1	48.8
Pancreas	4.58	6.23	9.05	14.1	24.7	48.8
Whole body	3.95	5.03	7.36	11.3	20.3	44.9
Spleen	3.87	5.05	7.59	12.0	20.7	41.1
Gall bladder wall	3.33	4.35	7.10	10.6	15.2	38.6
Stomach	3.19	4.50	6.80	7.14	11.3	35.3
Red marrow	3.07	3.63	5.03	6.74	10.9	22.1
Muscle	2.85	3.64	5.16	7.67	13.6	28.6
Colon wall, upper segment	2.71	3.38	5.29	7.72	13.4	26.2
Ovaries	2.69	3.44	5.19	7.90	13.6	27.3
Kidneys	2.36	3.22	5.00	7.78	13.8	29.3
Thyroid	2.33	3.04	5.26	8.30	14.9	27.1
Intestine	1.91	2.51	4.13	10.2	16.9	25.5
Colon wall, lower segment	1.85	2.47	4.28	6.65	12.1	26.0
Testes	1.78	2.45	4.17	6.47	12.1	23.8
Skin	1.34	1.55	2.51	3.91	7.07	16.1
Brain	0.70	0.88	1.46	2.36	4.10	9.46

Dose calculations were made with the standard MIRD method (MIRD Pamphlet No.1., Society of Nuclear Medicine, 1976). The Effective Dose Equivalence (EDE) was determined as specified in ICRP 53 (Ann.ICRP 18 (1-4), 1988). This value varied as follows: 1.45 x 10^{-2} mSv/MBq for adults, and 2.00 x 10^{-2} mSv/MBq, 2.85 x 10^{-2} mSv/MBq, 4.26 x 10^{-2} mSv/MBq, 7.81 x 10^{-2} mSv/MBq and 19.4 x 10^{-2} mSv/MBq for children aged 15, 10, 5 and 1 yr, respectively.

Radiation doses in women and in pregnant women
Estimated Absorbed Radiation Dose after administration of ^{99m}Tc-MAKRO-ALBUMON

Absorbed doses				
Organs	Pregnant w. µGy/MBq	Duration of pregnancy		
		3 months µGy/MBq	6 months µGy/MBq	9 months µGy/MBq
Lung	90.3	90.0	90.6	90.6
Bladder wall	53.8	55.3	62.3	136
Cardiac wall	11.9	11.9	11.9	11.9
Liver	10.9	10.9	10.9	10.9
Thymus	7.51	7.51	7.47	7.46
Adrenals	7.43	7.41	6.33	6.32
Breast	5.38	5.38	5.36	5.36
Uterus	5.89	5.09	2.56	2.40
Foetus		4.33	2.25	2.16
Placenta			1.51	1.20
Bone surface	5.96	5.97	5.74	5.75
Pancreas	6.15	6.11	5.40	5.37
Whole body	5.02	5.15	5.15	6.31
Spleen	5.15	5.12	4.29	4.29
Gall bladder wall	4.33	4.27	4.55	4.48
Stomach	4.30	4.19	1.64	4.18
Red marrow	3.60	3.59	3.41	3.42
Muscle	3.64	3.57	3.36	3.35
Colon wall, lower segment	3.41	3.48	2.16	1.87
Ovaries	3.40	2.81	1.73	1.88
Kidneys	3.18	3.14	2.73	2.71
Thyroid	2.91	2.91	3.05	3.04
Intestine	2.44	2.14	4.22	3.74
Colon wall, upper segment	2.47	2.15	1.96	1.32
Skin	1.57	1.58	1.64	1.66
Brain	0.84	0.84	0.77	0.78

Dose calculations were made with the standard MIRD method (MIRD Pamphlet No.1., Society of Nuclear Medicine, 1976). The Effective Dose Equivalence (EDE) was determined as specified in ICRP 53 (Ann.ICRP 18 (1-4),1988). This value was 1.87 x 10^{-2} mSv/Mbq for women, and 1.86 x 10^{-2} mSv/MBq, 1.87 x 10^{-2} mSv/MBq and 2.32 x 10^{-2} mSv/MBq, respectively, for pregnant women in 3, 6 or 9-months.

INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
Methode of preparation
Place the vial containing the freeze-dried powder into a lead case with a wall 3 mm thick. Then, with a sterile needle aseptically inject 2-8 ml of ^{99m}Tc pertechnetate with the required activity (maximum 3.7 MBq) through the rubber cap into the vial. Before withdrawing the syringe from the vial, withdraw 2-8 cm^3 of gas from the space above the solution to normalise the pressure in the vial. Do not use a breather needle. Shake the vial until complete dissolution of the freeze-dried powder. Let it stand at 20-25 °C for 20 minutes, with periodic shaking in the meantime. Complete the label provided and attaches it to the vial.
Quality control
The quality of labelling (radiochemical purity) can be checked according to the following procedure:
Method: Ascending thin-layer chromatography
Materials and reagents:
1. 2.0x20 cm silica gel (Kieselgel 60 DC-Alufolien)
2. Mobile phase: Acetone
3. Development tank
4. Syringe, needle, scissors, forceps and suitable equipment for activity measurements

Procedure:
Place a layer of the mobile phase 2 cm deep into the tank.
Drop a small volume (about 5-10 µl) of the preparation and of the reference ^{99m}Tc pertechnetate solution to cm^3 of the gel and dry it in air. Insert it in the vertical position into the tank and close the lid. Lower the strip into the mobile phase so that the test sample (drop site) is situated above the level of the solvent.
With forceps, remove the developed thin layer from the tank, dry it in the air and cut it into 1 cm strips.
The activities of the strips are measured with a NK-350 scaler coupled with an automatic sample sorter.
During development with acetone, the labelled preparation remains at the start line (R_f = 0.0) while the unbound pertechnetate migrates with the front line of the mobile phase (R_f = 0.9-1.0).
Determine the distribution of the radioactivity and identify the percentage of the total radioactivity bound to the preparation and that present as free pertechnetate or radioactive impurities.
Determination of labelling efficiency

$$^{99m}\text{Tc- MAKRO-ALBUMON (\%)} = \frac{\text{Activity (cpm) at } R_f = 0.0}{\text{Total activity of the thin layer (cpm)}} \times 100$$

Determination of radiochemical impurities:

$$\text{radiochemical impurities (\%)} = \frac{\text{Activity (cpm) at } R_f = 1.0}{\text{Total activity of the thin layer (cps)}} \times 100$$

The radiochemical purity should be at least 90% and the percentage of impurities should not be greater than 10%.