TECHNICAL LEAFLET

NAME OF THE MEDICINAL PRODUCT

NANO-ALBUMON

1 vial contains 1.0 mg Human Serum Albumin nano sized colloid

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Human Serum Albumin nano sized colloid	1.0 mg

Excipient(s):

Stannous(II) Chloride Dihydrate	0.2 mg
Sodium Phosphate Monobasic & Sodium Phosphate Dibasic	1.0 mg
Glucose	15.0 mg

More than 80% of the particles have a size less than 100 nm

Nano-Albumon is prepared from human serum albumin derived from human blood donations tested according to the EEC Regulations and found non reactive for:

- hepatitis B surface antigen (HBsAg)
- antibodies to human immunodeficiency virus (anti-HIV 1/2)
- antibodies to hepatitis C virus (anti-HCV)

PHARMACEUTICAL FORM

Powder for injection. For diagnostic use. Kit for radiopharmaceutical preparation. The kit contains a lyophilised, sterile, pyrogen free inactive preparation sealed in nitrogen atmosphere, ready for one-step labelling with Technetium–99m for radionuclide studies of the lymphatic system and bone marrow. 1 pack contains 6 multidose vials, six selfadhesive labels for stating the parameters of the labelled preparation, and instruction for use.

CLINICAL PARTICULARS

Therapeutic indications

This medicinal product is for diagnostic use only. The product is a cold radiopharmaceutical after reconstitution with sodium ^{99m}Tc-pertechnetate solution the agent may be used for:

Intravenous administration:

- Bone marrow scanning: serves to visualize defects in bone marrow distribution, expansion of active marrow into long bones occurring in myelofibrosis, haemolytic anaemia or myeloproliferative disorders. (The product is not suitable to study the haematopoietic activity of the bone marrow).
- Inflammation scanning in areas other than the abdomen.

Subcutaneous administration:

- Lymphatic scanning: to demonstrate integrity of the lymphatic system and differentiation of venous from lymphatic obstruction. It is useful definition of irradiation ports in radiotherapy and in the follow-up of lymphatic sequel to external and endolymphatic irradiation.

Posology and method of administration

Adult doses

For the labelling of one vial of lyophilised powder, use 1-5 ml of sterile ^{99m}Tc sodium pertechnetate solution with a maximum radioactivity of 5.5 GBq. Depending on the activity of the ^{99m}Tc solution used for labelling, the injection can be distributed into three-five portions. The recommended activity per examination for adults with a mean body weight of 70 kg is 150-200 MBq.

Recommended activities in adults are as follows:

Intravenous administration:

- Bone marrow scanning: 185-500 MBq. Images may be acquired 45-60 min. after administration.
- Inflammation imaging: 370-500 MBq. Dynamic imaging is performed immediately. Static imaging comprises an early phase, 15 min. post-injection and a washout phase, 30-60 min. post-injection.

Subcutaneous administration:

- The recommended activity for lymphoscintigraphy by single or multiple subcutaneous (interstitial) injection ranges from 18.5 - 110 MBq per injection site and depends on the anatomical areas to be investigated and upon the time interval between injection and imaging. The injected volume should not exceed 0.2 - 0.3 ml. A maximum volume of 0.5 ml per injection is critical.
  The injection site is given subcutaneously, after checking by aspiration, that a blood vessel has not been inadvertently punctured. When imaging the lower limbs, dynamic pictures are taken immediately following injection and static imaging 30-60 min. later.
  In parasternal lymph scanning, repeated injections and additional images may be required.
- Sentinel node detection: Three-five subcutaneous injections are administered near to the lesion. A volume 0.2-0.2 ml of 18 MBq is used per injection site. Imaging is commenced 20 min. after injection and repeated 1-5 hours later until the appearance of the first lymph node.

Pediatric doses

The activity for children may be calculated from the recommended range of adult activity and adjusted according to body weight or surface area.

However the Paediatric Task Group of EANM recommends calculating the administered activity from the body weight according to the following table.

Fraction of adult dose:

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

In very young children (up to 1 year) a minimum dose of 20 MBq (bone marrow scanning) is necessary in order to obtain images of sufficient quality.

In children, it is possible to dilute the product up to 1:50 with sodium chloride for injection. This agent is not intended for regular or continuous administration.

Contraindications

Hypersensitivity to the active substance. The use of ^{99m}Tc-human albumin colloidal particles is contraindicated in persons with a history of hypersensitivity to products containing human albumin. Adequate medication and reanimation equipment must therefore always be kept available during the investigation.

During pregnancy, lymphoscintigraphy involving the pelvis is strictly contraindicated due to the accumulation in lymph nodes.

Special warnings and precautions for use

The preparation without reconstitution with sodium ^{99m}Tc-pertechnetate must not be administered to patients.

The possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/anaphylactoid reactions should always be considered. The radionuclide-containing preparation should not be administered to a person with known hypersensitivity to human serum albumin. It cannot be administered to pregnant or lactating mothers or patients 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 child- bearing potential, the investigation should be performed during the first 10 days after the onset of menses. The labelled molecule can be used within 6 hours after reconstitution. The labelled preparation can be diluted, if needed, by the addition of sterile, isotonic saline. The reconstituted product should be stored at any temperature below 25 ^{o}C and protected against oxidants. Lymphoscintigraphy is not advised in patients with total lymphatic obstruction because of the potential radiation hazard at injection sites. The subcutaneous injection must be made without pressure into loose connective tissue. Prior to injection, an aspiration test should ascertain that no blood vessel was inadvertently punctured. The patient to be investigated should not eat anything for 4 hours before the investigation, and should eat only light food after the injection in order to facilitate the elimination of the radiopharmaceutical from the body. Radiopharmaceutical agents should only be used by qualified personnel with appropriate government authorisation for the use and manipulation of radionuclides. This radiopharmaceutical may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulation and/or appropriate licenses of local competent official organisations.

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.

Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Administration of local anaesthetic agents prior to administering the labelled preparation can disturb lymphatic uptake.

Iodinated contrast media used in lymphoangiography may interfere with lymphatic scanning using ^{99m}Tc-Nano-Albumon.

Pregnancy and lactation

Women of childbearing potential

When it is necessary to inject radiopharmaceuticals to women of childbearing potential, information should always be thought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainly 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 considered.

Pregnancy

Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only imperative investigations should-therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and fetus. Dose to the uterus arising for intravenous administration of 500 MBq of ^{99m}Tc-Nano-Albumon is 0.9 mGy. Dose to the uterus above 0.5 mGy will be regarded as a potential risk to the fetus. During pregnancy the subcutaneous administration of ^{99m}Tc-Nano-Albumon for lymphoscintigraphy is strictly contraindicated, due to the possible accumulation in pelvic lymph nodes.

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. If the administration is considered necessary, breast feeds should be banked prior to injection and the subsequent ones discarded after injection.

Breast feeding can be restarted 13 hours post injection.

Effects on ability to drive and use machines

Effects on ability to drive and use machines have not been described.

Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

When a protein-containing radiopharmaceutical such as ^{99m}Tc-Nano-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 each patient, exposure to ionising radiation must be justifiable on the basis of the 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 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 suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred. For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances. Occasionally hypersensitivity reactions (including very rare life-threatening anaphylaxis) may occur.

Overdose

In the event of an overdose of radioactivity being administered when using ^{99m}Tc-Nano-Albumon, no practical measure can be recommended to satisfactory diminish tissue exposure as the label is poorly eliminated in urine and faeces.

In the experiments with the Nano-Albumon preparation in rats no signs indicative of toxicity were observed. Based on allergic reaction cannot estimate overdose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ATC code: V09DB01

At the chemical concentrations and activities used for diagnostic procedures ^{99m}Tc-Nano-Albumon does not appear to exert any pharmacodynamic effects.

Pharmacokinetic properties

The Nano-Albumon colloidal product produced from human serum albumin consists of particles more than 80% of the particles have a size less than 100 nm Reticuloendothelial cells in liver, spleen as well as in bone marrow are responsible for blood clearance after intravenous injection. A small fraction of ^{99m}Tc radioactivity passes through kidneys and is eliminated in urine. The maximum concentration in the liver and spleen is reached after about 30 minutes, but in the bone marrow after only 6 minutes.

The proteolytic breakdown of the colloid begins immediately after its uptake by the RES, the products of degradation being excreted through the kidneys into

the bladder. After subcutaneous injection into connective tissue, 30-40 % of the administered ^{99m}Tc-Nano-Albumon are filtered into lymphatic capillaries whose main function is the drainage of proteins from the interstitial fluid back into the blood pool. The ^{99m}Tc-albumin colloidal particles are then transported along the lymphatic vessels to regional lymph nodes and main lymphatic vessels, and are finally trapped into the reticular cells of functionary lymph nodes. A fraction of the injected dose is phagocytized by histiocytes at the injection site. Another fraction appears in the blood and accumulates mainly in the RES of the liver, spleen and bone marrow; faint traces are eliminated via the kidneys.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: Pathological investigations during preclinical studies did not reveal pathological lesions in the organs of the laboratory animals. Mutagenicity, teratogenicity or carcinogenicity of the product has not been reported in the relevant literature. No animal death and no gross pathological changes at necropsy were noted after intravenous injection of 800 and 950 mg in mice and rats respectively. No local reactions were observed in either mice or rats subcutaneously injected with 1g/kg. These doses correspond to the contents of several tens of vials per kg body weight, compared to the human albumin colloid dose of 0.007 mg/kg generally used in nuclear medicine for diagnosis. Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

PHARMACEUTICAL PARTICULARS

List of excipients

Stannous(II) Chloride Dihydrate, Sodium Phosphate Monobasic, Sodium Phosphate Dibasic, Glucose

Incompatibilities

Non known.

Shelf life

The expiry date for the kit is 18 months. The labelled product should be used within 6 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 freeze-dried product is to be stored below 25°C. Do not store the reconstituted product above 25°C. Do not refrigerate or freeze. The reconstituted product should be stored in agreement 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

Sterile, colourless, 8 ml glass vials, European Pharmacopoeia Type I, 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

Name: MEDI-RADIOPHARMA LTD.
Address: 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-8664
Czech Republic: 88/174/91-C
Romania: 3489/2003/01

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Hungary: 01.03.1989./31. January, 2008.
Czech Republic: 03. 04.1994./13. September, 2006.
Romania: 125/1998/05. June, 2003.

DATE OF REVISION OF THE TEXT

January 2007

DOSIMETRY

(^{99m}Tc) Technetium decays with the emission of gamma radiation with an energy of 140 keV and a half life of 6 hours to (^{99}Tc) Technetium which can be regarded as quasi stable. The radiation doses absorbed by a patient weighing 70 kg, after intravenous injection of ^{99m}Tc-human albumin colloidal particles, are reported hereafter.

Adult and Children Category

Estimated Absorbed Radiation Dose after administration of Technetium ^{99m}Tc Nano-Albumon Injection

Organs	Absorbed doses					
	Adult µGy/MBq	Child				Newborn µGy/MBq
		15yrs µGy/MBq	10yrs µGy/MBq	5yrs µGy/MBq	1yr µGy/MBq	
Liver	16.0	20.3	30.2	42.2	75.6	161
Bladder wall	9.96	13.2	18.6	27.5	50.0	111
Gall bladder wall	8.08	10.1	15.2	22.7	31.4	73.0
Pancreas	6.37	7.98	11.9	18.0	30.8	63.6
Adrenals	6.31	7.71	11.4	16.3	28.2	59.0
Uterus	5.82	7.16	10.9	16.4	28.5	58.9
Ovaries	5.75	6.51	11.5	18.1	20.7	46.6
Red marrow	5.72	6.63	10.3	16.8	34.0	95.7
Bone surface	5.68	6.86	10.9	16.3	36.1	95.7
Intestinal wall, upper colon	5.57	7.22	10.8	17.3	28.2	60.1
Intestine	5.51	6.88	10.5	16.1	27.7	58.7
Kidneys	5.41	6.64	10.1	15.0	25.5	54.7
Myocardium	5.32	6.69	9.90	14.6	25.5	54.5
Intestinal wall, lower colon	5.20	6.56	10.3	14.9	26.9	53.4
Stomach	4.93	6.60	10.6	15.2	26.6	56.8
Lung	4.68	5.99	8.70	13.1	23.2	49.8
Whole body	4.48	5.49	8.42	13.0	23.3	52.4
Thymus	4.20	5.33	7.79	12.0	21.5	46.6
Spleen	4.11	5.44	8.27	12.1	20.9	45.3
Thyroid	4.05	5.14	8.14	13.0	23.1	49.5
Muscle	3.96	4.91	7.40	11.2	20.7	46.6
Testes	3.49	5.58	7.83	11.0	19.4	43.8
Brain	3.34	4.17	6.77	10.9	19.2	43.0
Breast	3.05	3.87	5.63	8.89	16.8	38.0
Skin	2.69	3.23	5.14	8.20	15.2	35.9

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: 6.24×10^{-3} mSv/MBq for adults and 7.64×10^{-3} mSv/MBq, 1.47×10^{-2}mSv/MBq, 2.05×10^{-2} mSv/MBq, 3.41×10^{-2}mSv/MBq and 7.32×10^{-2}mSv/MBq respectively, for children aged 15, 10, 5 and 1 years and for newborns.

Pregnancy Category

Estimated Absorbed Radiation Dose after administration of Technetium ^{99m}Tc-Nano-Albumon Injection

Organs	Absorbed doses			
	Pregnant women µGy/MBq	Duration of Pregnancy		
		3 months µGy/MBq	6 months µGy/MBq	9 months µGy/MBq
Breast	358	358	358	358
Myocardium	20.0	20.0	21.1	21.1
Thymus	10.3	10.3	9.16	9.16
Lung	8.11	8.11	8.39	8.39
Whole body	4.22	4.22	4.09	4.14
Bone surface	3.04	3.04	3.04	3.04
Skin	2.78	2.78	2.88	2.93
Liver	2.93	2.93	3.44	3.44
Stomach	2.68	2.68	3.31	3.31
Pancreas	2.57	2.57	2.53	2.53
Adrenals	2.05	2.05	2.03	2.03
Red marrow	1.89	1.89	1.89	1.89
Muscle	1.74	1.74	1.75	1.80
Spleen	1.72	1.72	1.71	1.71
Gall bladder wall	1.47	1.47	1.61	1.61
Thyroid	1.24	1.24	1.25	1.25
Kidneys	0.82	0.82	0.81	0.81
Intestinal wall, upper colon	0.49	0.49	1.59	1.78
Intestine	0.32	0.32	0.57	1.93
Uterus	0.127	0.126	0.641	0.830
Foetus		0.158	0.580	0.710
Placenta			1.26	1.56
Intestinal wall, lower colon	0.117	0.117	0.360	0.270
Ovaries	0.117	0.117	0.139	0.142
Brain	0.103	0.103	0.103	0.103
Bladder wall	0.081	0.081	0.088	0.082

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: 5.74×10^{-2} mSv/MBq for women and 5.74×10^{-2} mSv/MBq, 5.76×10^{-2} mSv/MBq and 5.76×10^{-2}mSv/MBq respectively, for pregnant women in 3, 6 or 9-months.

INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Method of preparation

Usual precaution regarding sterility and radioprotection should be respected.

1. Place the vial containing the lyophilised substance in a lead shield.
2. Inject sterile ^{99m}Tc-sodium pertechnetate solution Ph. Eur. (max. 5.5 GBq) aseptically into the vial in a volume of 1-5 ml. Before removing the syringe, withdraw an equal volume of the nitrogen gas to normalise the pressure in the vial. (Do not use a breather needle.)
3. Dissolve the lyophilised material by gently swirling, incubate at room temperature for 10 min., and then shake gently before injection. (Adjust the volume if necessary with oxidant-free physiological saline.)
4. After reconstitution, store the labelled Nano-Albumon at room temperature protected from light. Do not store the labelled product above +25°C.
5. Shake before withdrawing a dose
6. In no case should the preparation be left in contact with air.
7. The labelled preparation is to be used within 6 hrs. Within this period the total amount of radiochemical impurity is less than 10 %.

Quality control

The quality of labelling (radiochemical purity) can be controlled according to the following procedure:
Radiochemical purity at 10 min. after labelling. Both of the following methods can be used.

A - Free $^{99m}TcO_4^-$ by ascending paper chromatography

supportpaper	Whatman No. 1
solvent	methanol : water 85 : 15 v/v
time	1 hour
free $^{99m}TcO_4^-$	≤ 5.0 %
R_f	0.7 ± 10 %

B – Free $^{99m}TcO_4^-$ by ascending chromatography on ITLC-SG

support	ITLC-SG
solvent	methanol : water 85 : 15 v/v
time	5-10 min.
free $^{99m}TcO_4^-$	≤ 5.0 %
R_f	0.9 ± 10 %