AUSTRALIAN PRODUCT INFORMATION - DRAXIMAGE MACROSALB®
Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection

1 NAME OF THE MEDICINE

Albumin Aggregated

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Albumin Aggregated Injection for diagnostic use by intravenous injection.

Each 10 mL reaction vial contains 2.5 mg of albumin aggregated, 5 mg of albumin, 0.06 mg (minimum) stannous chloride (maximum stannous and stannic chloride 0.11 mg) and 1.2 mg of sodium chloride; the contents are in a lyophilized form under an atmosphere of nitrogen. Sodium hydroxide or hydrochloric acid has been used for pH adjustment. No bacteriostatic preservative is present.

The albumin was non-reactive when tested for Hepatitis B Surface Antigen (HB_sAg), antibodies to Human Immunodeficiency Virus (HIV-1/HIV-2), antibody to Hepatitis C Virus (anti-HCV) and Antigen to Human Immunodeficiency Virus (HIV-1). The aggregated particles are formed by denaturation of the albumin in a heating and aggregation process. Each vial contains 3 to 8 million particles. By light microscopy, more than 90% of the particles are between 10 and 70 micrometers, while the typical average size is 20 to 40 micrometers; none is greater than 150 micrometers.

Technetium Tc 99m Albumin Aggregated Injection for intravenous use is in its final dosage form when a sterile isotonic sodium pertechnetate solution is added to the vial (The radioisotope is not part of the kit). No less than 90% of the pertechnetate Tc-99m added to a reaction vial is bound to aggregate at preparation time and remains bound throughout the usage lifetime of the preparation (See Directions for Preparation under *Section 4.2 DOSE AND METHOD OF ADMINISTRATION*).

3 PHARMACEUTICAL FORM

Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection - DIAGNOSTIC - For Intravenous and Intraperitoneal Use.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Technetium Tc 99m Albumin Aggregated Injection is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients.

Technetium Tc 99m Albumin Aggregated Injection may be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (LeVeen) shunt patency.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adult Patients

The recommended dose range for intravenous injection in the average (70 kg) ADULT patient for lung imaging is 37 to 148 MBq (1 to 4 mCi) of Technetium Tc 99m Albumin Aggregated Injection after reconstitution with oxidant-free Sodium Pertechnetate Tc 99m Injection.

The suggested dosage range for intraperitoneal injection used in the average patient (70 kg) for peritoneovenous (LeVeen) shunt patency evaluation is 37 to 111 MBq (1 to 3 mCi). Adequate measures should be taken to assure uniform mixing with peritoneal fluid. Serial images of both the shunt and target organ should be obtained and correlated with other clinical findings. Alternatively, the drug may be administered by percutaneous transtubal injection. The suggested percutaneous transtubal (efferent limb) dosage range for the average patient (70 kg) is 12 to 37 MBq (0.3 to 1 mCi) in a volume not to exceed 0.5 mL.

The number of particles is to be reduced between 100,000 and 200,000 for patients with severe cardiovascular disease, with pulmonary hypertension accompanied by respiratory insufficiency or with right-to-left shunt.

Elderly patients

The dose for elderly is unknown. However, they have generally been treated with a similar dose as adult patients.

Pediatric patients

In pediatric patients, the suggested intravenous dose to be employed for perfusion lung imaging is in the range of 0.925 to 1.85 MBq per kilogram (25 to 50 μCi/kg) of body weight; a usual dose is 1.11 MBq per kilogram (30 μCi/kg), except in newborns, in whom the administered dose should be 7.4 to 18.5 MBq (200 to 500 μCi). Not less than the minimum dose of 7.4 MBq (200 μCi) should be employed for this procedure. The number of particles will vary with age and weight of the pediatric patient as indicated in Table 1.

Table 1 - Pediatric Radiation Dose from Tc 99m MACROSALB for Lung Imaging*

Age	Newborn		1 year		5 years		10 years		15 years	
Weight (kg)	3.5		12.1		20.3		33.5		55	
Max. recommended dose in MBq and mCi	MBq	mCi	MBq	mCi	MBq	mCi	MBq	mCi	MBq	mCi
	18.5	0.5	22.2	0.6	37	1	62.9	1.7	103.6	2.8
Range of particles administered	10,000 to 50,000		50, 000 to 150,000		200,000 to 300,000		200,000 to 300,000		200,000 to 700,000	
Absorbed radiation dose in milligray and rad for the maximum dose	mGy	rad	mGy	rad	mGy	rad	mGy	rad	mGy	rad
ORGANS										
Total body	0.6	0.06	0.3	0.03	0.31	0.031	0.48	0.048	0.41	0.041
Lungs	19	1.9	6.6	0.66	5.8	0.58	8.7	0.87	7.7	0.77
Liver	1.4	0.14	0.6	0.06	0.62	0.062	1.8	0.18	1.2	0.12
Bladder wall	2.1	0.21(1)	1.5	0.15(1)	3.1	0.31(2)	3.9	0.39(2)	4.1	0.41
Ovaries	0.38	0.038	0.2	0.02	0.19	0.019	0.44	0.044	0.41	0.041
Testes	0.31	0.031	0.13	0.013	0.19	0.019	0.2	0.02	0.36	0.036

(1) 2 hour voiding interval
(2) 4.8 hour voiding interval

***Assumptions:**
1. Used biologic data from Kaul *et al*., Berlin, 1973.
2. For the newborn, 1-year old, and 5-year old, the "S" values calculated from the preliminary phantoms of ORNL were used. The 10-year old, 15-year old and adult "S" values were taken from Henrichs *et al*., Berlin, 1980.

The number of particles available per dose of Technetium Tc 99m Albumin Aggregated Injection will vary depending on the physical decay of the technetium Tc-99m that has

occurred. The number of particles in any dose and volume to be administered may be calculated as follows:

$$V_a = \frac{D}{C \times F_r} \quad \text{and} \quad P = \frac{V_a}{V_{Tc}} \times N$$

Where:

V_{Tc} = volume of solution added to reaction vial
D = desired dose to be administered in MBq (mCi)
C = concentration at calibration time of sodium pertechnetate solution to be added to the reaction vial in MBq/mL (mCi/mL)
V_a = volume to be administered in mL
P = number of particles in dose to be administered
F_r = fraction of technetium Tc-99m remaining after the time of calibration (see Table 7)
N = number of particles per vial. The number of particles per vial for each lot is shipped with the product.

In PEDIATRIC patients, the suggested intravenous dose to be employed for perfusion lung imaging is in the range of 0.925 to 1.85 MBq per kilogram (25 to 50 μCi/kg) of body weight; a usual dose is 1.11 MBq per kilogram (30 μCi/kg), except in newborns, in whom the administered dose should be 7.4 to 18.5 MBq (200 to 500 μCi). Not less than the minimum dose of 7.4 MBq (200 μCi) should be employed for this procedure. The number of particles will vary with age and weight of the pediatric patient as indicated in Table 1.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

Using proper shielding, parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. Mix the contents of the vial by gentle inversion just prior to withdrawing a patient dose.

Gently mix the contents of the syringe just before injection. If blood is drawn into the syringe, any unnecessary delay prior to injection may lead to clot formation. For optimum results and because of rapid lung clearance of the radiopharmaceutical, it is suggested that the patient be positioned under the imaging apparatus before administration. Slow injection is recommended. Lung imaging may begin immediately after intravenous injection of the radiopharmaceutical. Due to high kidney uptake, imaging later than one-half hour after administration will yield poor results.

RADIATION DOSIMETRY

The estimated absorbed radiation doses to an average ADULT patient (70 kg) from an intravenous injection of 148 MBq (4 mCi) of Technetium Tc 99m Albumin Aggregated Injection are shown in Table 2.

Table 2- Absorbed Radiation Doses[1]

Organs	mGy/148 MBq	rad/4 mCi
Total body	0.6	0.06
Lungs	8.8	0.88
Liver	0.72	0.072
Spleen	0.68	0.068
Kidneys	0.44	0.044
Bladder Wall		
2 hr. void	1.2	0.12
4.8 hr. void	2.2	0.22
Testes		
2 hr. void	0.24	0.024
4.8 hr. void	0.26	0.026
Ovaries		
2 hr. void	0.3	0.03
4.8 hr. void	0.34	0.034

[1] Method of calculation: "S" Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

In PEDIATRIC patients, the radiation absorbed doses using the maximum recommended dose for lung imaging are based on 1.85 MBq (50 μCi) per kilogram of body weight [except in the newborn where the maximum recommended dose of 18.5 MBq (500 μCi) is used] and are shown in Table 1, which lists the maximum dose for pediatric patients from newborn to adults. Note the recommendations regarding number of particles to be administered.

Table 3 represents the absorbed radiation dose resulting from the intraperitoneal administration of 111 MBq (3 mCi) of Technetium Tc 99m Albumin Aggregated.

Table 3 - Absorbed Radiation Doses*

Organs	Shunt Patency (Open)		Shunt Patency (Closed)	
	mGy	rad	mGy	rad
Lung	6.9	0.69	1.68	0.168
Ovaries & testes	0.18 to 0.3	0.018 to 0.03	1.68	0.168
Organs in the peritoneal cavity	-	-	1.68	0.168

Total body	0.36	0.036	0.57	0.057

***Assumptions:**
Calculations for the absorbed radiation dose are based upon an effective half-time of 3 hours for the open shunt and 6.02 hours for the closed shunt and an even distribution of the radiopharmaceutical in the peritoneal cavity with no biological clearance.

DIRECTIONS FOR PREPARATION

NOTE: Use aseptic procedures throughout and take precautions to minimize radiation exposure by use of suitable shielding. Waterproof gloves should be worn during the preparation procedure.

Before reconstituting a vial, it should be inspected for cracks and/or a melted plug or any other indication that the integrity of the vacuum seal has been lost.

To prepare Technetium Tc 99m Albumin Aggregated Injection:

1. Remove the protective disc from a reaction vial and swab the rubber septum with either an alcohol swab or a suitable bacteriostatic agent to disinfect the surface.

2. Place the vial in a suitable lead vial shield which has a fitted cap. Obtain 2 to 8 mL of a sterile pyrogen-free Sodium Pertechnetate Tc 99m Injection using a shielded syringe. Sodium pertechnetate Tc 99m solutions containing an oxidizing agent are not suitable for use. The recommended maximum amount of Tc-99m to be added to a reaction vial varies with the number of particles per vial and is shown in Table 4. Other calculations for reconstitution are permitted provided that the patient dose remains within the range prescribed in this package insert (See Dosage and Administration).

Table 4 - Maximum Tc 99m to be Added Based on Vial Particle Number

Particles per Vial	Maximum Tc 99m to be added per vial*
3 million to 4 million	3.7 GBq (100 mCi)
5 million	4.44 GBq (120 mCi)
6 million to 8 million	6.85 GBq (185 mCi)

*Calculate the amount of radioactivity /vial required to maintain the number particles per dose within a recommended range [for adults 200,000 to 700,000, and for pediatric patients follow Table 1].

3. Using a shielded syringe, add the Sodium Pertechnetate Tc 99m Injection to the reaction vial aseptically.

4. Place the lead cap on the vial shield and mix the contents of the shielded vial by repeated gentle inversion until all the material is suspended. Avoid formation of foam. Using proper shielding, the vial should be visually inspected to ensure that the suspension is free of foreign matter before proceeding. Do not administer if foreign particulates are found in the preparation. To ensure maximum tagging, allow the preparation to stand for 15 minutes after mixing.

5. Assay the product in a suitable calibrator, record the radioassay information on the label with radiation warning symbol, and attach it to the vial shield.

6. The radiochemical purity of the finished preparation should be determined prior to patient administration. The radiochemical purity should not be less than 90%.

7. Withdrawals for administration must be made aseptically using a sterile needle (18 to 21 gauge) and syringe. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be vented. If repeated withdrawals are made from the vial, replacement of the contents with air should be minimized.

8. Retain the reconstituted product in the lead vial shield with cap in place during its in-use shelf life. Store the reconstituted product at 2 ºC to 8 ºC (36 ºF to 46 ºF) when not in use and discard within 12 hours depending on the number of particles per vial, the activity added at reconstitution and the final dose to be administered to the patient (See Dosage and Administration).

4.3 CONTRAINDICATIONS

Technetium Tc 99m Albumin Aggregated Injection should not be administered to patients with severe pulmonary hypertension.

The use of Technetium Tc 99m Albumin Aggregated Injection is contraindicated in persons with a history of hypersensitivity reactions to products containing albumin.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

Although adverse reactions specifically attributable to Technetium Tc 99m Albumin Aggregated Injection have not been noted, the literature contains reports of deaths occurring after the administration of albumin aggregated to patients with pre-existing severe pulmonary hypertension. Instances of hemodynamic or idiosyncratic reactions to preparations of Technetium Tc 99m Albumin Aggregated have been reported.

General Precautions

The contents of the kit before reconstitution are not radioactive. However, after the sodium pertechnetate Tc-99m is added, maintain adequate shielding of the reconstituted product.

In patients with right-to-left heart shunts, additional risk may exist due to the rapid entry of albumin aggregated into the systemic circulation. The safety of this agent in such patients has not been established. Hypersensitivity reactions are possible whenever protein-containing materials such as pertechnetate labeled albumin aggregated are used in man. Epinephrine, antihistamines, and corticosteroids should be available for immediate use.

The intravenous administration of any particulate materials such as albumin aggregated imposes a temporary small mechanical impediment to blood flow. While this effect is probably physiologically insignificant in most patients, the administration of albumin aggregated is possibly hazardous in acute *cor pulmonale* and other states of severely impaired pulmonary blood flow.

The components of the kit are sterile and non-pyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation.

Contents of the vials are intended only for use in the preparation of Technetium Tc 99m Albumin Aggregated Injection and are *NOT* to be administered directly to the patient.

The technetium Tc-99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, sodium pertechnetate Tc-99m containing oxidants should not be employed.
The preparation contains no bacteriostatic preservative. Technetium Tc 99m Albumin Aggregated Injection should be stored at 2 ºC to 8 ºC and discarded 12 hours after reconstitution.

Technetium Tc 99m Albumin Aggregated Injection is physically unstable and consequently the particles settle with time. Failure to agitate the vial adequately before use may result in non-uniform distribution of radioactive particles.

If blood is drawn into the syringe, unnecessary delay prior to injection may result in clot formation *in situ*.

Do not use if clumping of the contents is observed.

Technetium Tc 99m Albumin Aggregated Injection, as well as other radioactive drugs, must be handled with care. Once sodium pertechnetate Tc-99m is added to the vial, appropriate safety measures must be used to minimize radiation exposure to clinical personnel. Care must also be taken to minimize the radiation exposure to patients in a manner consistent with proper patient management.

Radiopharmaceuticals 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 license the use of radionuclides.

Pathogen Safety

This product contains albumin, a derivative of human blood. When medicines are made from human blood or plasma, measures are put in place to prevent infection transmission. Despite this, 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 recommended that the name and batch number of the product be recorded in order to document the batches utilized.

Use in the elderly

No data available.

Pediatric use

The lowest possible number of particles should be used in right-to-left shunting, in neonates, and in severe pulmonary disease.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Changes in the biological distribution of Technetium Tc 99m Albumin Aggregated could be induced by different medicinal products.

- Theoretical considerations should be given to toxicological interactions with various chemotherapeutics, heroin, busulfan, nitrofurantoin and methysergide.

- Pharmacologic interaction may be expected with bronchodilators, heparin and chemotherapeutic agents. Interaction with chemotherapeutic agents could result in an increased bone marrow uptake.

- Pharmaceutical interaction could result from the concomitant administration of cations, such as magnesium, leading to flocculation (aggregation) of Albumin Aggregated particles.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No long term animal studies have been performed to evaluate whether Technetium Tc 99m Albumin Aggregated Injection affects fertility in males or females.

Use in pregnancy

Pregnancy Category C

Since adequate reproduction studies with technetium Tc 99m Albumin Aggregated Injection have not been performed in animals to determine whether this drug affects fertility in males and females, has teratogenic potential or has other adverse effects on the foetus, this radiopharmaceutical preparation should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards to the foetus and safer alternative procedures are not available.

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 minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Use in lactation

Technetium-99m is excreted in human milk. Interruption to breast feeding is necessary after the administration of Technetium Tc 99m Albumin Aggregated Injection for a period of at least 12h.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The literature contains reports of deaths occurring after the administration of albumin aggregated to patients with pre-existing severe pulmonary hypertension. Instances of hemodynamic or idiosyncratic reactions to preparations of Technetium Tc 99m Albumin Aggregated have been reported (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Reporting suspected adverse effects

Healthcare professionals should report any suspected adverse reactions at www.tga.gov.au/reportingproblems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Immediately following intravenous injection, more than 80% of the albumin aggregated is trapped in the pulmonary alveolar capillary bed. The imaging procedure can thus be started as soon as the injection is complete. 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, and are imaged as areas of reduced photon density.

Organ selectivity is a direct result of particle size. Below 1 to 10 micrometers, the material is taken up by the reticuloendothelial system. Above 10 micrometers, the aggregates become lodged in the lung by a purely mechanical process. Distribution of particles in the lungs is a function of regional pulmonary blood flow.

The albumin aggregated is sufficiently fragile for the capillary micro-occlusion to be temporary. Erosion and fragmentation reduce the particle size, allowing passage of the aggregates through the pulmonary alveolar capillary bed. The fragments are then accumulated by the reticuloendothelial system.

Lung to liver ratios greater than 20:1 are obtained in the first few minutes post-injection. Elimination of the Technetium Tc 99m Aggregated Albumin from the lungs occurs with a half-life of about 2 to 3 hours. Cumulative urinary excretion studies show an average of 20% elimination of the injected technetium Tc 99m dose 24 hours post-administration.

Following administration of Technetium Tc 99m Albumin Aggregated by intraperitoneal injection, the radiopharmaceutical mixes with the peritoneal fluid. Clearance from the peritoneal cavity varies from insignificant, which may occur with complete shunt blockage, to very rapid clearance with subsequent transfer into the systemic circulation when the shunt is patent.

Serial images should be obtained of both the shunt and lung (target organ). However, an adequate evaluation of the difference between total blockage of the shunt and partial blockage may not be feasible in all cases.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

The early use of radiolabelled MACROSALB in humans already gave initial data on the pharmacokinetic profile of this compound. As indicated above, after intravenous injection the lung capillary beds efficiently extract the particles from the bloodstream with (almost) no activity detectable in other organs. Distribution studies have confirmed these earlier data and showed that 87% of the dose will be trapped in the lungs of patients (Furth et al., 1965).

Some pathological conditions may lead to disturbances in this distribution pattern. A case report describes the extrapulmonary uptake in the spleen after lung scanning without any right-left shunting being present. Partial fragmentation of the particles and subsequent phagocytosis by leucocytes which then are trapped in splenic sinusoids is considered the only possible explanation (Hellin et al., 1992).

When used for venoscintigraphic purposes (vide infra) in the presence of circulatory defects, such as superior and inferior vena cava obstruction, hepatic localization of MACROSALB has been described as a consequence of alternate pathways of venous return (Kolla et al., 1989; Rieker et al., 1993).

Likewise, significant radioisotope uptake in the lungs, brain, spleen and both kidneys was demonstrated in 2 patients with liver cirrhosis associated with marked hypoxemia (Shijo et al., 1989). The increased passage of MACROSALB particles through widened pulmonary capillaries (pulmonary telangiectasia) rather than the occurrence of small pulmonary arterio-venous shunts is considered as the cause of this aberrant distribution pattern.

A number of reports exist which describe measurable concentrations of (assumed free pertechnetate) radioactivity in the expressed breast milk of mothers with babies (Cranage and Palmer, 1985; Ahlgren 1985; Rose 1997). Cranage showed that the fraction of the original dose which entered into the milk was 8×10^{-5}/ml at 4 hours after administration, while at 24 hours post-injection this was decreased to $0.1\text{-}0.2 \times 10^{-5}$/ml. Based on these data it was calculated that the cumulative absorbed dose for the baby varied from 6.1 mrad to 0.2 mrad when starting breastfeeding 4 hours after the injection or 24 hours after the injection respectively. The authors consider a 24-hour break in feeding ideal from a radiation-protection viewpoint as this reduces both the internal radiation caused by milk consumption and the external radiation received by the infant whilst being nursed by the mother. Others have suggested 12 hours is an adequate interval (Stabin 2000).

Metabolism and Excretion

The major mechanism of the clearance from the lungs of the particles is breakup of large aggregates into smaller ones capable of passing through the capillaries to enter the main bloodstream. Therefore the smaller the particle size, the more rapid the clearance. This aggregate breakup can be caused by hemodynamic pressure and pulsation as well as by vessel contraction (Davis, 1975). In commercial preparations of 131I-MACROSALB it was shown that the percent activity remaining in the lungs 24 hours after injection correlates well with the percentage of activity on particles greater than 50 μm in the initial dose.

Early clinical studies (Wagner et al., 1964) showed that in 4 patients the half-time of 131I-MACROSALB for the disappearance from the lungs varied from 5-10 hours. More detailed experiments followed shortly (Furth, 1965) and demonstrated that the

disappearance of radioactivity from the lungs of 9 patients was multi-exponential with a mean biological half-time of the rapid initial component of 0.25 days and of the second component, of 3.2 days. Total serum and protein bound activity also disappeared in a multi-exponential fashion and half-time values for both types of activity were virtually identical in man with a mean value of 0.44 day for the initial phase and 4.0 days for the second phase. It could not be made clear whether the slower component represented a typical compartment in the body or the disappearance of a distinctly different material. Urinary investigations also revealed that about 95% of the radioactivity was iodide and by seven days a total of 72 ± 9% had been accounted for in the urine. There was no significant foetal excretion in 2 patients studied for 72 hours.

In a study including 24 patients and various batches of a commercial product of 131I-MACROSALB, a significant variation between batches and between patients was observed (Spencer, 1972) with the retention half-time varying from 7-31 hours. It was postulated that this variability was related to the progress of the underlying disease. Altered hemodynamics, for example, could seriously influence both the fragmentation of the initial particles as well as the rate of removal of the particle fragments from the lungs.

Pharmacokinetic results obtained initially with 99mTc-MACROSALB showed that the switch from 131I-MACROSALB to 99mTc-MACROSALB did not significantly influence the elimination half-life in the lungs as this was established at approximately 11 hours, using the 2nd-generation preparation (including stannous chloride). However, due to the more rapid radioactive decay of 99mTc the effective half-life was calculated at 236 ± 26 min. in seven patients (Chandre et al., 1973). Equal to the results described above, urinary excretion proceeded only slowly with 33% of the injected dose excreted in the first 24 hours and 50-60% in 72 hours. The radioactivity detected in the blood at 15 min., 4 hours, and 24 hours did not reveal much variation and was always less than 0.015% of the injected dose.

After the initial fragmentation of the albumin particles, the fragments are transported by the bloodstream towards the liver where they are trapped by the reticuloendothelial cells and subsequently are catabolized following the regular pathway for protein metabolism (Bocci, 1990). This pathway includes the presence of various serine-, cysteine-, aspartic- and metallo-proteinases in body fluids that can potentially hydrolyze any protein, including albumin. Parallel to the presence of these enzymes proteinase inhibitors (acute phase proteins) occur and which modulate the activity of the proteinases. However, the most important aspect is intracellular catabolism following phagocytosis by the reticuloendothelial cells or after internalization of the albumin-receptor complex formed by individual albumin molecules. Subsequently intracellular proteinases will be responsible for the catabolism of the albumin molecules. Early studies have shown this catabolism to proceed very rapidly in man with a half-time of approximately 20 minutes for the albumin accumulated in the liver (Taplin et al., 1963). At the same time, this rapid rate of proteolytic digestion and radiomarker release from the liver can be slowed by a factor of 2 or more by the simultaneous administration of unlabeled aggregates.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 – Qualitative and quantitative composition.

6.2 INCOMPATABILITIES

Please refer to Section 4.5 “Interactions with other medicines and other forms of interactions”.

6.3 SHELF LIFE

The finished preparation should be discarded 12 hours after reconstitution. Do not use the kit beyond the expiry date stamped on the box.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

The vials are sealed under an atmosphere of nitrogen. The unreconstituted reaction vials should be stored at 2 ºC to 25 ºC.

After labeling with technetium Tc-99m, store the reconstituted product at 2 ºC to 8 ºC when not in use and discard within 12 hours (See Directions for Preparation).

The reconstituted product should be stored during its in-use shelf life in a lead vial shield with cap in place.

6.5 NATURE AND CONTENT OF CONTAINER

DRAXIMAGE MACROSALB® **(ARTG # 315902)** comprises:

10 multi-dose glass vials. Each vial contains a non-radioactive sterile, non-pyrogenic lyophilized mixture of:

Albumin Aggregated	2.5 mg
Albumin	5.0 mg
Sodium Chloride	1.2 mg
Stannous Chloride Dihydrate	0.1 mg

- 2 x 5 Radiation Labels;
- 1 Package Insert.

HCl and/or NaOH has been used for pH adjustment. The vials are sealed under an atmosphere of nitrogen.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The residual materials may be discarded in the ordinary trash, provided the radioactivity in the vials and syringes measures no more than background with an appropriate low-range survey meter. All identifying labels should be destroyed before discarding.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure and CAS Number are unidentified.

Technetium Tc-99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies is listed in Table 5.

Table 5 - Principal Radiation Emission Data

Radiation	Mean % / Disintegration	Mean Energy (keV)
Gamma	89.07	140.5

EXTERNAL RADIATION

The specific gamma ray constant for technetium Tc-99m is 0.78 R/mCi-hr at 1 cm.

The first half value layer is 0.017 cm of lead. A range of values for the relative attenuation of the radiation resulting from the interposition of various thicknesses of lead is shown in Table 6. For example, the use of 0.25 cm thickness of lead will attenuate the radiation emitted by a factor of about 1,000.

Table 6 - Radiation Attenuation by Lead (Pb) Shielding

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 7.

Table 7 - Physical Decay Chart: Tc-99m half-life 6.02 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	5	0.562
1	0.891	6	0.501
2	0.794	8	0.398
3	0.708	10	0.316
4	0.631	12	0.251

*Calibration Time

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled.

8 SPONSOR

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