**BRACCO DIAGNOSTICS™**

**MAGROTEC®**
**Kit for the Preparation of Technetium To 99m Albumin Aggregated**
**Diagnostic—For Intravenous Use**

## DESCRIPTION

Macrotec is a sterile, nonpyrogenic, lyophilized preparation of albumin aggregated. Each 5 mL vial of Macrotec contains 1.5 mg of Albumin Aggregated, 10.0 mg Albumin Human, 0.07 mg (minimum) stannous chloride ($SnCl_2 \cdot 2H_2O$) and 0.19 mg total tin, maximum (as stannous chloride, $SnCl_2 \cdot 2H_2O$ ), 1.8 mg of sodium chloride with trace amounts of sodium acetate, acetic acid and hydrochloric acid. Macrotec contains no preservatives. The pH of the reconstituted product is between 3.8 and 8.0.

The aggregated particles are formed by denaturation of Albumin Human in a heating and precipitation process. Each vial contains 2-7 million partcles, 90% of which are between 10 and 90 microns in size. The average size is 20 to 40 microns; no particles are greater than 150 microns.

Reconstitution of Macrotec with sterile sodium pertechnetate To 99m forms an aqueous suspension of Technetium Tc 99m Albumin Aggregated for diagnostic use by intravenous injection. No less than 90% of the pertechnetate Tc 99m added to the reaction vial is bound to the aggregates at preparation time and remains bound throughout the 6-hour lifetime of the suspension.

## PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by Isomeric transition with a physical half-life of 6.02 hours.[1] The principal photon that Is useful for detection and imaging studies is listed in Table 1.

**TABLE 1**

Principal Radiation Emission Data

| Radiation | Mean % per Disintegration | Mean Energy (keV) |
|---|---|---|
| Gamma-2 | 89.07 | 140.5 |

[1]Kocher, David C., 'Radioactive Decay Data Tables", DOE/TIC-11026, (1981) p.108.

### External Radiation

The specific gamma ray constant for To 99m is 0.78 R/hour-millicurie at 1 cm. The first half value layer is 0.017 cm of lead (Pb). A range of values for the relative attenuation of the radiation resulting from the interposition of various thicknesses of Pb Is shown in Table 2. For example, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

**TABLE 2**

Radiation Attenuation by Lead 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-* |

To correct for physical decay of technetium To 99m, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

**TABLE 3**

| Physical Decay Chart: Tc 99m half-life 6 02 hours | | | |
|---|---|---|---|
| Hours | Fraction Remaining | Hours | Fraction Remaining |
| 0* | 1.000 | 8 | 0.398 |
| 1 | 0.891 | 9 | 0.355 |
| 2 | 0.794 | 10 | 0.316 |
| 3 | 0.708 | 11 | 0.282 |
| 4 | 0.631 | 12 | 0.251 |
| 5 | 0.562 | 18 | 0.126 |
| 6 | 0.501 | 24 | 0.063 |
| 7 | 0.447 | | |

*Calibration time

**CLINICAL PHARMACOLOGY**

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 have been used (see DOSAGE AND ADMINISTRATION), 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 correspondingly decreased accumulation of the radioactive particles, and these areas are imaged as areas of decreased photon density.

Following administration of technetium Tc 99m albumin aggregated by intraperltoneal 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.

Organ selectivity is a direct result of particle size. Below 1-10 microns the material is taken up by the reticuloendothelial system. Above 10 microns the aggregates become lodged in the lung capillaries by a purely mechanical process.

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. Normally, the clearance half-time of the particles from the lungs is 2 to 3 hours.

Studies have shown that when Technetium Tc 99m Albumin Aggregated is injected peripheral to the suspected point of the disease process, the radioactive aggregated particles collect at the sites of endothelial damage and/or clot formation.

**INDICATIONS AND USAGE**

**Lung Imaging**

Macrotec (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated) is a lung Imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and children. It is useful in the early detection of pulmonary emboli and in the evaluation of the status of the pulmonary circulation in such conditions as pulmonary neoplasm, pulmonary tuberculosis and emphysema.

**Shunt Imaging**

Technetium Tc 99m albumin aggregated may be used in adults as an imaging agent to aid in the evaluation of peritoneo-venous (LeVeen) shunt patency.

**Isotopic Venograpny**

Macrotec is also indicated for use in isotopic venography as an adjunct in the screening, diagnosis and management of deep vein thrombosis in the lower extremities.

Combined isotopic venography of the lower extremities and the pulmonary vasculature may be performed.

**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 human serum albumin.

**WARNINGS**

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.

**PRECAUTIONS**

**General**

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 kept available for immediate use.

The intravenous administration of any particulate material 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 Macrotec (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated) are sterile and non-pyrogenic. It is essential to follow directions carefully and adhere to strict aseptic procedures during preparation. Contents of the vial 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 contents of the kit before preparation are not radioactive. However, after the sodium pertechnetate Tc 99m is added, adequate shielding of the final preparation must be maintained.

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 2-8°C and discarded 6 hours after formulation.

Technetium Tc 99m Albumin Aggregated Injection is a physically unstable suspension 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.

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.

As In the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management and to minimize radiation exposure to clinical personnel.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
No long-term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc 99m Albumin Aggregated Injection affects fertility in males or females.

**Pregnancy Category C**
Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Albumin Aggregated Injection. It is also not known whether Technetium To 99m Albumin Aggregated Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium To 99m Albumin Aggregated Injection should be given to a pregnant woman only if clearly needed. Ideally, examinations using radiopharmaceuticals, especially those elective in nature, in women of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses.

**Nursing Mothers**
Technetium Tc 99m Is excreted in human milk during lactation. Therefore, formula-feedings should be substituted for breast-feedings.

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

## ADVERSE REACTIONS
Although adverse reactions specifically attributable to the 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.

## DOSAGE AND 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. 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. Slow injection is recommended. Imaging may begin immediately after intravenous injection of Technetium Tc 99m Albumin Aggregated; follow-up imaging should be performed as needed.

**Lung Imaging**
The recommended intravenous dose range for the average ADULT patient (70 kg) is 37 MBq to 148 MBq (1 to 4 mCi) Technetium Tc 99m Albumin Aggregated after reconstitution with oxidant-free Sodium Pertechnetate Tc 99m Injection. The recommended number of particles per single injection is 200,000-700,000 with suggested number being approximately 350,000.

The number of particles available per megabecquerel (millicurie) 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 available in any specific dose may be estimated by calculating the number of particles per milliliter.

In PEDIATRIC patients, the suggested intravenous doses employed for perfusion lung imaging are in the range of 0.925 MBq to 1.85 MBq per kilogram (25 to 50 uCi/kg) o( body weight with a usual dose of 1.11 MBq per kilogram (30 uCi/kg), except in newborns in whom the administered dose should be 7.4 MBq to 18.5 MBq (200-500 uCI). A minimum dose of 7.4 MBq (200 uCi) should be employed for this procedure. The number of particles administered will vary with age and weight of the child as Indicated in Table 4.

**Table 4.**

| Particle Size and Dose | | | | | |
|---|---|---|---|---|---|
| Ages | Newborn | 1 Year | 5 Years | 10 Years | 15 Years |
| Weight (kg) | 3.5 | 121.1 | 20.3 | 33.5 | 55.0 |
| Usual Administered Dose MBq (mCi) | 7.4 (0.2) | 14.8 (0.4) | 22.2 (0.6) | 37 (1.0) | 59.2 (1.6) |
| Range of Particles Administered (in thousands) | 10-50 | 50-150 | 200-300 | 200-300 | 200-700 |

**Isotopic Venography**

The usual dose for unilateral or bilateral isotopic venography of the lower extremities is 74 to 148 MBq (2-4 mCi) Technetium Tc 99m Albumin Aggregated Injection per limb, injected intravenously peripheral to the suspected areas of venous clot formation.

For isotopic venography of the lower extremities, the patient should be supine and properly positioned under the scintillation camera. For unilateral or bilateral imaging of the lower extremities, a tourniquet should be applied just above the malleolus of each leg to be imaged in order to promote deep vein filling. For simultaneous bilateral imaging, doses should be administered from separate syringes. Rapid sequential scintiphotographs should then be taken along the course of venous flow from the calf to the abdomen. If retention of radioactivity ("hot spots") occurs in the calf region, the patient should be instructed to exercise the lower extremities by flexion and extension of the knees and ankles; reimaging should be performed after about 15 minutes.

Following vein imaging, lung imaging may be performed without need of additional Technetium Tc g9m Albumin Aggregated.

**LeVeen Shunt Patency**

The suggested intraperitoneal dosage range used in the average patient 70 kg) for peritoneo-venous (LeVeen) shunt patency evaluation is 37 to 1.11 megabecquerels (1 to 3 millicuries). 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 megabecquerels (0.3 to 1.0 millicurie) in a volume not to exceed 0.5 mL,

**Radiation Dosimetry**

The estimated absorbed radiation doses[1] 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 5.

**TABLE 5**

| Adult Absorbed Radiation Doses | | |
|---|---|---|
| Tissue | mGy/148 MBq | rads/4 mCi |
| Total Body | 0.60 | 0.060 |
| 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 | 0.30 | 0.030 |
| 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 uCi) per kilogram of body weight (except in the newborn where the maximum recommended dose of 18.5 MBq (500 uCI) is used) and are shown in Table 6, which lists the maximum dosage for children up to the age of 15 years. Note the recommendations regarding number of particles to be administered.

**Table 6.**

| Pediatric Absorbed Dose | | | | | |
|---|---|---|---|---|---|
| Ages | Newborn | 1 year old | 5 year old | 10 year old | 15 year old |
| Weight (kg) | 3.5 | 121.1 | 20.3 | 33.5 | 55.0 |
| Maximum Recommended Dose MBq (mCi) | 18.5 (0.5) | 22.2 (0.6) | 31 (1.0) | 62.9 (1.7) | 103.6 (2.8) |
| Absorbed Dose [mGy (rad)/max dose ] Total Body | 0.6 (0.06) | 0.3 (0.03) | 0.31 (0.031) | 0.48 (0.048) | 0.41 (0.41) |
| 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)* | 1.5 (0.15)* | 3.1 (0.31)** | 3.9 (0.39)** | 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) |

*2 hour voiding interval **4.8 hour voiding Interval

NOTE: DOSES TO TESTES, OVARIES AND BLADDER INCREASE WITH VOIDING INTERVAL. Method of Calculation:

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 and 15-year old S values were taken from Henrichs et al., Berlin, (1980).

The following table represents the absorbed radiation dose resulting from the intraperitoneal administration of 111 megabecquerels (3 millicuries) of technetium Tc 99m Albumin Aggregated.

**Table 7.**

| | Absorbed Radiation Dose | | | |
|---|---|---|---|---|
| Organ | Shunt Patency (Open) | | Shunt Patency (Closed) | |
| | mGy | rads | mGy | rads |
| Lung | 6.9 | 0.69 | 1.68 | 0.168 |
| Ovaries & Testes | 0.18 to 0.30 | 0.018 to 0.030 | 1.68 | 0.0168 |
| 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.

**HOW SUPPLIED**
Macrotec (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated) is supplied as a kit containing 10 reaction vials (5 mL size), 10 pressure sensitive labels and 1 package insert.

**Storage**
Store the Macrotac kit between 2° and 8° C. The reconstituted preparation should be refrigerated since the product does not contain a preservative.

When reconstituted with sodium pertechnetate Tc 99m, Macrotec must be used within 6 hours.

**PROCEDURES FOR RECONSTITUTION OF MACROTEC Procedural Precautions**
The contents of the Macrotec reaction vial are sterile and nonpyrogenic. Aseptic procedures should be used during reconstitution of Macrotec and the withdrawal of doses for intravenous administration. The Introduction of air into the vial during the reconstitution step should be avoided. Since the vial contains nitrogen to prevent oxidation of the complex, the vial should not be vented. If repeated withdrawals are made from the vial, the contents should not be replaced with air.

The Minitec (Technetium Tc 99m) Generator may be used as the source of sodium pertechnetate Tc 99m solution; other sources which have been shown by the user to be compatible with the ingredients of Macrotec (Kit for the Preparation of TechneUum Tc 99m Albumin Aggregated) may also be used.

**ReconstItutIon**
1. Waterproof gloves should be worn during the preparation procedure.
2. Allow the contents of the reaction vial to come to room temperature.
3. Place the Macrotec vial in an appropriate lead shield with a fitted cover.
4- Swab the rubber closure of the reaction vial with a germicide.
5. Using a shielded syringe, slowly inject 1 to 3 mL [up to 1850 MBq (50 mCi)] of sterile sodium pertechnetate Tc 99m solution into the reaction vial. In determining the amount of technetium Tc 99m to be used, the labeling efficiency, number of patients, administered radioactive dose and radioactive decay must be taken into account. NOTE: If sodium pertechnetate Tc 99m solution must be diluted for use with Macrotec (Kit for the Preparation of Technetium Tc 99m Albumin Aggregated) only Sodium Chloride Injection USP (without preservatives) should be used,
6. Secure the lead shield cover. Shake the vial gently in order for the lyophilized material to form a suspension. Avoid formation of foam. To ensure maximum tagging, allow the preparation to stand for 6 minutes after mixing.
7. Record the time and date of preparation and the radioconcentration and volume of the suspension on the pressure-sensitive label.
8. Affix the pressure-sensitive label to the shield.
9. Using proper shielding, examine vial contents. The suspension must be uniform and free from large aggregates, flakes or particulate matter.
10. Maintain adequate shielding of the radioactive preparation including the use of appropriate shielded syringes.

11. Radioassay of Technetium Tc 99m Albumin Aggregated may be accomplished conveniently with the use of an ionizatlon chamber-type dose calibrator.

The U.S. Nuclear Regulatory Commission has approved this reagent kit for distribution to persons licensed to use byproduct material Identified in §35.200 of 10 CFR Part 35, to persons who hold an equivalent license Issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

Manufactured for
Bracco Diagnostics Inc.
Princeton, NJ. 08543
by E.R. Squibb & Sons Inc.
New Brunswick, N.J. 08903
Printed In USA Revised November 1994 J3-436R