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רופא/ה רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלון לרופא בעקבות "אימוץ עלון כלשונו" עבור התכשיר:

## FROSSTIMAGE/DRAIMAGE KIT FOR THE PREPARATION OF TC99M (MAA)

חומר פעיל :

Human Serum Albumin 2.5 mg/vial

התוויה מאושרת:

Lung imaging evaluation of pulmonary perfusion.

להלן עלון לרופא כפי שעודכן מעלון אסמכתא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן צהוב משמעותו החמרה):

### SUMMARY OF PRODUCT CHARACTERISTICS

## FROSSTIMAGE/DRAIMAGE KIT FOR THE PREPARATION OF TC99M (MAA)

### For Intravenous Use

Solution for Injection containing  
Human Serum Albumin 2.5 mg/vial

### INDICATIONS AND USAGE

#### Lung imaging evaluation of pulmonary perfusion.

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 paediatric patients.

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

### DESCRIPTION

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, 5.0 mg of albumin human, 0.1 mg of stannous chloride dihydrate and 1.2 mg of sodium chloride; the contents are in a lyophilized form under an atmosphere of nitrogen. Sodium hydroxide and/or hydrochloric acid is used for pH adjustment prior to lyophilization so that the pH of the reconstituted radiopharmaceutical is 5.2 to 6.0.

No bacteriostatic preservative is present.

The human serum albumin was non-reactive when tested for Hepatitis B Surface Antigen (HBsAg), 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 human 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 sterile isotonic sodium pertechnetate solution is added to each vial. Not less than 90% of the pertechnetate Tc 99m added to a reaction vial is bound to aggregates at preparation time and remains bound throughout the 8-hour lifetime of the preparation.

### ACTION

Immediately following intravenous injection, more than 80% of the aggregated albumin 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 reticulo-endothelial 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 aggregated albumin is sufficiently fragile for 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 indicate an average of 20% elimination of the injected technetium Tc 99m dose within 24 hours after administration.

### 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 also been reported.

## PRECAUTIONS

### General

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.

In patients with right to left heart shunts, additional risk may exist due to the rapid entry of aggregated albumin 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-labelled aggregated albumin are used in man. Epinephrine, antihistamines, and corticosteroids should be available for immediate use.

The intravenous administration of any particulate materials such as aggregated albumin imposes a small temporary mechanical impediment to blood flow. While this effect is probably physiologically insignificant in most patients, the administration of aggregated albumin 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 labelling 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 °C to 8 °C and discarded 8 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, any 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.

### **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 and Teratogenicity**

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Albumin Aggregated Injection. It is also not known whether Technetium Tc 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 Tc 99m Albumin Aggregated Injection should be given to a pregnant woman only if clearly needed.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman 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.

### **Paediatric Use**

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

## **ADVERSE REACTIONS**

The literature contains reports of deaths occurring after the administration of aggregated albumin 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 **WARNINGS**).

### **Reporting of suspected adverse reactions**

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (<https://sideeffects.health.gov.il>).

## PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.<sup>1</sup> The principal photon that is useful for detection and imaging studies is listed in Table 1.

**Table 1**

**Principal Radiation Emission Data**

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

### External Radiation

The specific gamma ray constant for technetium-99m is  $5.44 \mu\text{C}\cdot\text{Kg}^{-1}\cdot\text{MBq}^{-1}\cdot\text{hr}^{-1}$  (0.78 R/mCi-hr) at 1 cm. The first half value layer is 0.017 cm of lead. To facilitate control of the radiation exposure from megabecquerel amounts of this radionuclide, the use of a 0.25 cm thickness of lead will attenuate the radiation emitted by a factor of about 1,000. A range of values for the relative attenuation of the radiation resulting from the interposition of various thicknesses of lead is shown in Table 2.

**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	$10^{-4}$

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

**Table 3**

**Physical Decay Chart of Technetium 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

## RADIATION DOSIMETRY

The estimated absorbed radiation doses<sup>2</sup> to various organs of 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 4.

**Table 4**

**Estimated Absorbed Radiation Doses**

<b>Organ/Tissue</b>	<b>mGy/per148 MBq</b>	<b>rads/4 mCi</b>
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		
2.0 hr. void	1.2	0.12
4.8 hr. void	2.2	0.22
Testes		
2.0 hr. void	0.24	0.024
4.8 hr. void	0.26	0.026
Ovaries		
2.0 hr. void	0.30	0.030
4.8 hr. void	0.34	0.034

In paediatric patients, the radiation absorbed doses using the maximum recommended dose for lung imaging are based on 1.85 MBq/kg (50 µCi/kg) of body weight (except in the newborn where the maximum recommended dose 18.5 MBq [500 µCi] is used) and are shown in Table 5, which lists the maximum dose for paediatric patients from newborn to adults. Note the recommendations regarding the number of particles to be administered.

## DOSAGE AND ADMINISTRATION

The recommended intravenous dose range for the average (70 kg) adult patient 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 range of particle numbers for a single injection is 200,000 to 700,000 with the recommended number being approximately 350,000. Depending on the activity added and volume of the final reconstituted product, the volume of the dose may vary from 0.2 to 1.4 mL.

In paediatric patients, the suggested intravenous dose to be employed for perfusion lung imaging is in the range of 0.925 MBq 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 MBq 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 paediatric patient as indicated in Table 5.

**Table 5**

**Paediatric Radiation Dose from Tc 99m MAA  
For Lung Imaging\***

Age	Newborn		1 year		5 years		10 years		15 years	
Weight (kg)	3.5		12.1		20.3		33.5		55.0	
Maximum recommended dose in megabecquerels and millicuries	MBq	mCi	MBq	mCi	MBq	mCi	MBq	mCi	MBq	mCi
		18.5	0.5	22.2	0.6	37	1.0	62.9	1.7	103.6
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 rads for the maximum dose	mGy	rads	mGy	rads	mGy	rads	mGy	rads	mGy	rads
ORGAN										
Total body	0.60	0.06	0.30	0.03	0.31	0.031	0.48	0.048	0.41	0.041
Lungs	19.00	1.9	6.60	0.66	5.80	0.58	8.70	0.87	7.70	0.77
Liver	1.40	0.14	0.60	0.06	0.62	0.062	1.80	0.18	1.20	0.12
Bladder wall	2.10	0.21 <sup>(1)</sup>	1.50	0.15 <sup>(1)</sup>	3.10	0.31 <sup>(2)</sup>	3.90	0.39 <sup>(2)</sup>	4.10	0.41
Ovaries	0.38	0.038	0.20	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	0.20	0.02	0.36	0.036

(1) 2.0 hour voiding interval

(2) 4.8 hour voiding interval

**\*Assumptions:**

- Used biologic data from Kaul *et al.*, Berlin, 1973. (3)
- 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. (4)

The number of particles available per millicurie dose of technetium Tc 99m will vary depending on the physical decay of the technetium that has occurred. The number of particles available in any dose and volume to be administered may be calculated by means of the following formulas:

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

Where:

$V_a$  = Volume to be administered in mL

$D$  = Desired dose to be administered in MBq (mCi)

$C$  = Concentration at calibration time of the sodium pertechnetate solution to be added to the reaction vial in MBq/mL (mCi/mL)

$F_r$  = Fraction of technetium Tc 99m remaining after the time of calibration (see Table 3)

$P$  = Number of particles in dose to be administered

$N$  = The number of particles per vial

$V_{Tc}$  = The volume of solution added to the reaction vial

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. Slow injection is recommended. For optimum results and because of rapid lung clearance, it is suggested that the patient be positioned under the imaging apparatus before administration. 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.

### **DIRECTIONS FOR PREPARATION**

The preparation of Technetium Tc 99m Albumin Aggregated Injection may be accomplished by the following procedure. Use aseptic procedure throughout and take precautions to minimize radiation exposure by the 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.

It is anticipated that any Tc 99m generator approved in Canada would be suitable as a source of sodium pertechnetate Tc 99m, however, complete data is not available to confirm this. Jubilant DraxImage Inc. should be contacted for any available information.

The Tc 99m pertechnetate eluate should be less than 2 hours old and should be obtained from a generator which has been eluted within the last 24 hours.

To prepare Technetium Tc 99m Albumin Aggregated Injection:

1. Remove the protective disc from the reaction vial and swab the closure with an alcohol swab.
2. Place the vial in a suitable lead vial shield which has a minimum wall thickness of 3 mm (1/8 inch) and a fitted lead cap. Obtain 2 to 8 mL of sterile, non-pyrogenic sodium pertechnetate Tc 99m using a shielded syringe.

The recommended maximum amount of technetium Tc 99m (at the time of elution) to be

added to a reaction vial is 5.18 gigabecquerels (140 mCi). Sodium pertechnetate Tc 99m solutions containing an oxidizing agent are not suitable for use.

- Using a shielded syringe, aseptically add the sodium pertechnetate Tc 99m solution to the reaction vial, while avoiding the build up of excessive pressure in the vial. Pressure build up may be avoided by injecting several milliliters of pertechnetate solution into the reaction vial, then withdrawing several milliliters of nitrogen gas (present to prevent oxidation of the complex) into the syringe. The procedure is repeated as necessary until the entire amount of pertechnetate is added to the vial and normal pressure is established within the vial.
- 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 the formation of foam. Using proper shielding, the vial should be visually inspected to ensure that the suspension is free of foreign matter before proceeding; if it is not, the radiopharmaceutical should not be used. To ensure maximum radiolabelling, allow the preparation to stand for 15 minutes after mixing at 2° C to 8 °C.
- Assay the product in a suitable calibrator, record the radioassay information on the label which has a radiation warning symbol. Also note the time and date of preparation. Apply the label to the vial shield.
- The radiochemical purity of the finished preparation should be determined prior to patient administration. The radiochemical purity should not be less than 90%.
- Withdrawals for administration must be made aseptically using a sterile needle (18to 21 gauge) and syringe. Since the vials contain nitrogen, the vials should not be vented. If repeated withdrawals are made, the replacement of the contents of the vial with air should be minimized.
- The finished preparation should be discarded after 8 hours. It should also be retained during its life in a lead vial shield with the lead cap in place.

## Radiochemical Purity

### Chromatographic Methods

The following procedure describes a series of simple steps for running chromatograms. Steps 1to 6 describe the method for determining free pertechnetate in a mixture of chelated and reduced technetium. The TLC procedure requires the following:

Solid phase: ITLC-SG  
Solvent: Acetone (for determination of pertechnetate)

#### Step 1

Add 1 mL of the required solvent to an 18 mm x 150 mm test tube. Stopper and allow the atmosphere in the tube to equilibrate for 1 minute.

## Step 2

Place a drop (approximately 0.02 mL) of the radioactive solution on a 1 cm x 10 cm chromatographic strip at a pencil mark 1 cm from one end of the strip, which is the origin. A simple way to do this is to use a standard 1 mL tuberculin syringe with a 25 gauge needle and dispense one small drop. Discard the needle and syringe after use. Instead of a tuberculin syringe a 20 microliter disposable micropipette can also be used to dispense 0.02 mL.

Immediately dry the spot using a gentle stream of nitrogen gas. Do not use compressed air since this tends to cause pertechnetate formation.

## Step 3

Develop the chromatogram by placing it, with the origin down into the solvent, in the previously equilibrated test tube. Stopper the test tube. The test tube should be kept upright, ideally in a test tube rack. Development requires about 10 minutes for ITLC-SG strips.

## Step 4

When the solvent front has climbed to the top of the strip, remove it with forceps and allow it to dry. The strips can be dried by placing them radioactive side up on a disposable non-porous pad at room temperature.

The bound and reduced fractions stay at the origin while free pertechnetate  $TcO_4^-$  migrates to the front  $R_f$  0.85 to 1.0.

## Step 5

Cut the dried strip 2 cm from the solvent front end. The short piece is marked *Part II* and the long piece is marked *Part I*. Count the pieces in a suitable counter and determine the percentage of free pertechnetate according to the following formula:

$$\text{Percent } TcO_4^- = \frac{\text{Counts in Part II} \times 100}{\text{Counts in Part I} + \text{Part II}}$$

## Step 6

Store all waste radioactive strips for 48 hours before disposing of them as non-radioactive waste. Store used chromatographic solvents in a similar fashion.

## HOW SUPPLIED

### MAA

Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection

Product No. 500150

Available in cartons containing 10 reaction vials, each reaction vial containing, in lyophilized form, sterile and non-pyrogenic:

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

The vials are sealed under an atmosphere of nitrogen.

Labels with radiation warning symbol and a package insert are supplied in each carton.

### STORAGE

The unreconstituted reaction vials should be stored at 2 °C to 25°C. After labelling with technetium Tc 99m, the radiopharmaceutical should be stored at 2 °C to 8 °C.

### EXPIRY

**The expiry date of the product is indicated on the packaging materials.**

The finished preparation should be discarded 8 hours after reconstitution. Do not use the kit beyond the expiry date stamped on the box.

### MANUFACTURER

JUBILANT DRAXIMAGE INC.,  
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### REGISTRATION HOLDER

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### MARKETING AUTHORISATION NUMBER

**134-62-29990-00**

### REFERENCES

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