PRODUCT MONOGRAPH

Technescan MAG3™

Kit for the Preparation of Technetium Tc 99m Mertiatide

Lyophilized Powder for Solution, 5-10mCi

Radiodiagnostic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

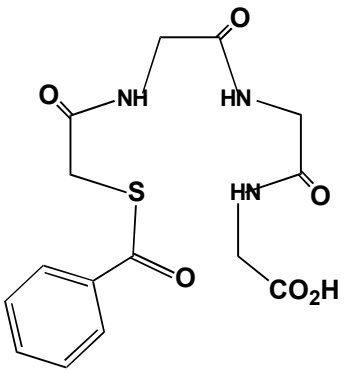
SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous injection	Lyophilized Powder for Solution, 5-10 mCi	The kit contains lactose monohydrate, stannous chloride dihydrate, sodium tartrate dihydrate and total tin expressed as stannous chloride. *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.*

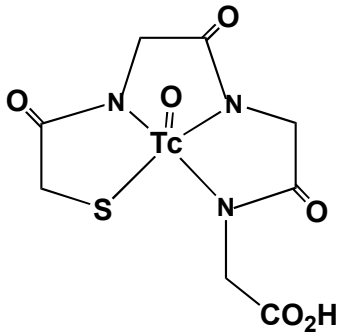
DESCRIPTION

Technescan MAG3™ is a kit for the preparation of technetium Tc 99m mertiatide, a diagnostic radiopharmaceutical. It is supplied as a sterile, non-pyrogenic, lyophilized powder. Each vial contains betiatide (N-[N-[N-[(benzoylthio) acetyl]glycyl]glycyl] -glycine). After reconstitution with sterile sodium pertechnetate Tc 99m injection, the technetium Tc 99m mertiatide (disodium[N-[N-[N-(mercaptoacetyl) glycyl]glycyl] glycinato (2-)-N,N',N'',S'] oxotechnetate (2-)) which is formed is suitable for intravenous administration.

Each 10 milliliter vial contains 1 milligram betiatide, 0.05 milligram (minimum) stannous chloride dihydrate ($SnCl_2 \cdot 2H_2O$) and 0.2 milligram (maximum) total tin expressed as stannous chloride dihydrate ($SnCl_2 \cdot 2H_2O$), 40 milligrams sodium tartrate dihydrate ($Na_2C_4H_2O_6 \cdot 2H_2O$), and 20 milligrams lactose monohydrate. Prior to lyophilization, sodium hydroxide or hydrochloric acid may be added for pH adjustment. The pH of the reconstituted drug is between 5.0 and 6.0. No bacteriostatic preservative is present. The contents are sealed under argon. Technescan MAG3™ kits are light sensitive and must be protected from light. Betiatide and technetium Tc 99m mertiatide have the following structural formulas:



Betiatide



Technetium Tc 99m Mertiatide

Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.01 hours[1]. The principal photon that is useful for detection and imaging is listed in Table 1.

Table 1. Principal Radiation Emission Data[1]

Radiation	Mean % per Disintegration	Energy (keV)
Gamma-2	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 thickness of lead (Pb) for technetium Tc 99m is 0.023cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. For example, the use of 0.27 cm of Pb will decrease the external radiation exposure by a factor of about 1000.

Table 2. Radiation Attenuation by Lead Shielding[2]

Shield Thickness Pb, (cm)	Coefficient of Attenuation
0.023	0.5
0.09	10^{-1}
0.18	10^{-2}
0.27	10^{-3}

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

Table 3. Physical Decay Chart: Technetium Tc 99m; Half-Life 6.01 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.780	10	0.316
-4	1.586	11	0.281
-3	1.413	12	0.251
-2	1.259	13	0.223
-1	1.122	14	0.199
0*	1.000	15	0.177
1	0.891	16	0.158
2	0.794	17	0.141
3	0.708	18	0.125
4	0.631	19	0.112
5	0.562	20	0.100
6	0.501	21	0.0888
7	0.446	22	0.0791
8	0.398	23	0.0705
9	0.354	24	0.0628

* Calibration Time

INDICATIONS AND CLINICAL USE

Technetium Tc 99m mertiatide is a renal imaging agent for use in the diagnosis of congenital and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients (*see* **WARNINGS AND PRECAUTIONS, Pediatrics**). It is a diagnostic aid used to assess renal perfusion, size, position, and configuration, renal function (including differential renal function), renal angiograms, and renogram curves for whole kidney and renal cortex. Technetium Tc 99m mertiatide may also be used as an indirect measurement of effective renal plasma flow.

CONTRAINDICATIONS

None known.

However, patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container should advise their physician (*see* **DOSAGE FORM, COMPOSITION AND PACKAGING**). <

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Radiopharmaceuticals should be used under the supervision of 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.

General

The product should be administered under the supervision of a physician who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The Tc 99m labeling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Hence, sodium pertechnetate Tc 99m containing oxidants should not be employed.

The contents of the kit are not radioactive. However, after the sodium pertechnetate Tc 99m is added, adequate shielding of the final preparation must be maintained to minimize radiation exposure to occupational workers and patients.

Contents of the reaction vial are intended only for use in the preparation of technetium Tc 99m mertiatide and are NOT to be administered directly to the patient until the reconstitution process has been completed.

To help reduce the radiation dose to the bladder, as well as other target organs, the patient should increase his or her fluid intake (unless medically contraindicated) and void as often as possible after the injection of technetium Tc 99m mertiatide for six hours after the imaging procedure.

Technetium Tc 99m mertiatide should not be used more than six hours after preparation.

Carcinogenesis and Mutagenesis

No long term animal studies have been performed to evaluate the carcinogenic or mutagenic potential of technetium Tc 99m mertiatide, or whether this drug affects fertility in males or females. As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

Contamination

The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product: Toilet should be used instead of urinal. Toilet should be flushed several times after use.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

Special Populations

Pregnant Women:

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of women of childbearing capability should be performed during the first ten days following the onset of menses.

Since adequate reproduction studies have not been performed in animals to determine whether technetium Tc 99m mertiatide affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this radiopharmaceutical preparation should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards.

Nursing Women:

Where an assessment of the risk to benefit ratio suggests the use of the product in lactating mothers, formula feeding should be substituted for breastfeeding for a period of at least 24 hours.

Pediatrics (0 - 16 years of age):

Safety and effectiveness in pediatric patients under the age of 30 days (neonates) have not been established. However, studies performed to date in older pediatric patients have not demonstrated any pediatric-specific problems that would limit the use of technetium Tc 99m mertiatide in this population.

Geriatrics (> 65 years of age):

No data available.

ADVERSE REACTIONS

The following adverse reactions have been reported: nausea, vomiting, wheezing, dyspnea, itching, skin rash, tachycardia, hypertension, shaking chills, fever, and seizure.

DRUG INTERACTIONS
No data available.

DOSAGE AND ADMINISTRATION
Technetium Tc 99m Mertiatide Injection is administered intravenously. The suggested dose range employed in the average adult patient (70 kg) for renal function and imaging studies is 185 MBq (5 mCi) to 370 MBq (10 mCi). In pediatric patients, the recommended dose range is 2.6 MBq/kg (70 μCi/kg) to 5.2 MBq/kg (140 μCi/kg), with a minimum imaging dose of 37 MBq (1 mCi).

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

Administration
The patient dose should be measured using a suitable radioactivity calibration system immediately prior to administration.

Image Acquisition and Interpretation

Patient Preparation
It is important that the patient be well-hydrated prior to the examination, since the state of hydration will affect tracer excretion and the shape of the renogram curve. Increased hydration will decrease the radiation dose to the bladder, and the patient should be advised to empty the bladder frequently after the examination.

Image Acquisition
Imaging is generally performed with the patient in a supine position, although the sitting position may be employed. A gamma camera interfaced with a computer is used. Images are acquired in the posterior projection for evaluation of native kidneys and in the anterior projection for evaluation of renal allografts. Imaging is performed with a 20% window centered around 140 keV, with a low energy all purpose (LEAP) collimator for adults or a low energy high resolution (LEHR) collimator for pediatric patients.

A radionuclide angiogram may be obtained during the first minute after injection of technetium Tc 99m mertiatide, with a constant frame duration of 1-3 seconds. Between 1 and 2 minutes following injection, a renal image is obtained, followed by continuous collection of analog images every 1 to 2.5 minutes from 2 to 30 minutes following injection. Continuous digital data are collected at a rate of 20 seconds per frame for 30 minutes. From the digital data, activity versus time (renogram) curves are generated from regions of interest which may be placed around the whole kidney and/or around the renal cortex. All regions are corrected for soft tissue background. Digital data acquired between 1 and 2 minutes or between 2 and 3 minutes may be used to calculate differential renal function. If pooling of tracer is noted in the collecting structures on final supine images and if not clinically contraindicated, a static renal image may be recorded in the upright position after obtaining post-void bladder images.[3]

Renogram Interpretation

Figure 1 is a schematic representation of a normal renogram. The renogram can be divided into three phases. The initial phase occurs when the tracer is first entering the kidney, resulting in a rapid rise in activity; this represents renal blood flow. In the second phase, rate of renal tracer increase is slower, and represents renal extraction of tracer from the blood. There is a peak at the end of phase 2, which in normal kidneys occurs between 2 and 5 minutes. The third phase, occurring after the peak, represents tracer excretion and drainage.

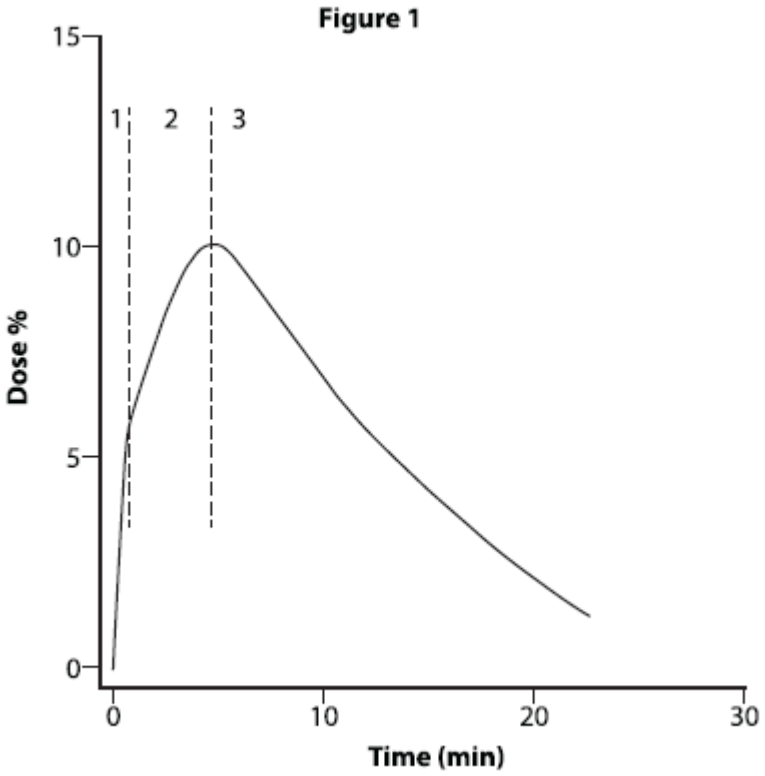


Image Interpretation

Following injection of tracer, there is simultaneous and symmetric delivery to and uptake of the tracer by normal kidneys. The two minute image shows good cortical delineation. By four minutes, there is accumulation of tracer within intrarenal collecting structures, followed by drainage of tracer into the bladder. Functional abnormalities of the renal arteries, renal parenchyma or collecting structures can produce alterations in the rate of delivery of technetium Tc 99m mertiatide to the kidneys, the rate of renal excretion or the drainage pattern.[4]

Instructions for Preparation and Use

Note: Read complete directions thoroughly before starting preparation procedure.

The components of the reagent vial are sterile and non-pyrogenic. It is essential that the user follows the directions carefully and adheres to strict aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers during the addition of pertechnetate solution and the withdrawal of doses for patient administration.

Procedural Precautions and Notes

1. **NOTE:** Do not use Tc 99m eluate more than 6 hours after its elution from the generator.

2. The water bath used for heating the contents of the reaction vial must be at a continuous rolling boil during the heating step of the preparation procedure. The vial should be in direct contact with the rolling boil of the water bath, and the level of the bath must be at least even with the level of the contents of the vial.

3. The temperature of a lead incubation shield should be allowed to reach the temperature of the water bath before incubating the reaction vial. The shield should be designed so that water flows through the interior of the shield.

   Note 1: Use aseptic technique and wear waterproof gloves during the entire preparation procedure and during subsequent patient dose withdrawals from the reaction vial.

   Note 2: Make all transfers of sodium pertechnetate Tc 99m solutions with an adequately shielded syringe and shielding around the vial during the useful life of the radioactive product.

   Note 3: The radiochemical purity of reconstituted technetium Tc 99m mertiatide must be checked prior to administration to the patient.

Procedure For The Preparation Of Technetium Tc 99m Mertiatide

1. Prepare a rolling boil water bath containing a vial shield with openings cut in it to allow the water to circulate through the shield. The openings should be oriented to prevent radiation leakage.

2. Place the reaction vial in a lead dispensing shield fitted with a lid and with a minimum wall thickness of 1/8 inch.

3. Swab the rubber stopper of the reaction vial with an appropriate antiseptic. Insert a filter-containing venting needle (provided) through the vial stopper. Inject 4 to 10 mL of sodium pertechnetate Tc 99m solution containing 740 MBq (20 mCi) to 3.70 GBq (100 mCi) into the vial. If required, use non-bacteriostatic normal saline to dilute the sodium pertechnetate Tc 99m solution to the desired concentration prior to addition to the vial.

NOTE: Make sure the water bath is at boiling temperature before adding the sodium pertechnetate Tc 99m to the reaction vial.

4. Immediately following the addition of sodium pertechnetate Tc 99m solution to the reaction vial, withdraw the syringe plunger to a volume of 2 mL, thus removing 2 mL of argon gas and adding 2 mL of filtered air to the vial. The air is required to oxidize excess stannous ion. Remove both needles from the vial.

   NOTE: The addition of 2 mL of air is required to prevent the progressive formation of technetium Tc 99m labeled impurities.

5. Invert the reaction vial several times to obtain complete mixing.

6. Immediately transfer the reaction vial to the water bath. Place it inside the lead shield which has been equilibrated to the temperature of the boiling water bath. Allow the reaction vial to incubate for 10 minutes.

   NOTE: The reaction vial **MUST** be placed in the boiling water bath within 5 minutes of the addition of sodium pertechnetate Tc 99m solution.

7. Remove the reaction vial from the boiling water bath and place it in the lead dispensing shield. Allow the contents of the vial to cool for approximately 15 minutes to reach body temperature. Using proper shielding, the vial contents should be visually inspected.

The solution should be clear and free of particulate matter. If not, the preparation should not be used.

8. Assay the reaction vial using a suitable radioactivity calibration system. Record the date, time, total technetium Tc 99m activity, volume, and technetium Tc 99m concentration on the radioassay information label and affix the label to the lead dispensing shield.

9. **The radiochemical purity of the reconstituted solution must be checked prior to administration to the patient. If the radiochemical purity is less than 90%, the product must not be used.**

10. Store the reaction vial containing the technetium Tc 99m mertiatide at controlled room temperature 20-25°C (68-77°F) until use. **The technetium Tc 99m mertiatide preparation must be used within six hours of preparation.**

Directions for Quality Control

The radiochemical purity of the radiopharmaceutical product should be determined prior to administration to the patient.

RECOMMENDED METHOD FOR DETERMINATION OF RADIOCHEMICAL PURITY OF TECHNESCAN MAG3™

Required Materials:
Waters Sep-Pak® C18 Cartridges, part #51910
200 proof ethanol
0.9% Sodium Chloride Injection, USP
0.001 N hydrochloric acid*
1:1 ethanol/saline solution**
Disposable culture tubes or vials, minimum 15 mL capacity
Ion chamber for measurement of radioactive samples
Disposable Syringes: 10 mL, no needle required. 1 mL with needle.

*May be prepared by diluting 1 mL of 0.10 N hydrochloric acid to 100 mL with Water for Injection, USP, or by other appropriate dilution of more concentrated hydrochloric acid. For example, 0.1 mL of 36% (~11.6 N) hydrochloric acid diluted to a total volume of 1,150 mL.

**Prepared by mixing equal volumes of the 200-proof ethanol and 0.9% Sodium Chloride Injection, USP.

Preparation of Sep-Pak® Cartridge
1. Using a 10 mL syringe, push 10 mL of 200-proof ethanol through the Sep-Pak® cartridge. Discard the eluate.

2. Similarly, flush the cartridge with 10 mL of the 0.001 N hydrochloric acid. Discard the eluate.

3. Drain the cartridge by pushing 5 mL of air through the cartridge with the syringe. Discard the eluate.

Sample Analysis
1. Apply 0.1 mL of the technetium Tc 99m mertiatide preparation to the head of the cartridge through the longer end of the cartridge using a 1 mL syringe with needle.

   Note: The cartridge and all solutions eluted from it will be radioactive after this step.

2. With a disposable 10 mL syringe, slowly push 10 mL of 0.001N hydrochloric acid through the cartridge. Collect this fraction in a culture tube or vial for counting.

3. Similarly, elute the cartridge with 10 mL of the 1:1 ethanol/saline solution. Be sure that this solution is pushed through the cartridge slowly so that the elution occurs in a dropwise manner. Collect this 10 mL fraction in a second culture tube or vial for counting.

4. Place the Sep-Pak® cartridge in a third culture tube or vial for counting.

Counting

1. Assay the activity of the first sample elution in an ion chamber. This fraction contains the hydrophilic impurities (free pertechnetate, technetium tartrate, etc.) and a fraction of reduced-hydrolyzed technetium.

2. Assay the activity of the second elution. This fraction contains the technetium Tc 99m mertiatide complex.

3. Assay the activity of the Sep-Pak® cartridge in the third culture tube or vial. This component contains the remaining reduced-hydrolyzed technetium and non-elutable impurities.

Calculations

1. Percent technetium Tc 99m mertiatide =

$$\frac{\text{Activity of 2}^{\text{nd}}\text{ (ethanol/saline) fraction}}{\text{Total activity of all three fractions}} \times 100\%$$

2. Percent hydrophilic impurities =

$$\frac{\text{Activity of 1}^{\text{st}}\text{ (0.001N HCl acid) fraction}}{\text{Total activity of all three fractions}} \times 100\%$$

3. Percent non-elutable impurities =

$$\frac{\text{Activity remaining on Sep-Pak® cartridge}}{\text{Total activity of all three fractions}} \times 100\%$$

ALTERNATE METHOD FOR DETERMINATION OF RADIOCHEMICAL PURITY OF TECHNESCAN MAG3™

Required Material:
Chromatography Chamber
Whatman Chromatography Paper Cellulose Grade 3 MM CHR
Acetone AR grade
Water for Injection
Ion chamber for measurement of radioactive samples.

Preparation, Chromatography and Results
The procedure for determining the radiochemical purity of Tc 99m labeled mertiatide involves two separate determinations: (1) free pertechnetate (TcO_2) is measured using Whatman 3MM paper and Acetone. Both reduced-hydrolyzed technetium (RHTc) and Tc 99m labeled mertiatide remain at the origin while free pertechnetate migrates to the solvent front. (2) The second system uses Whatman 3MM paper with water to detect and measure RHTc. The RHTc remains

at the point of sample application while both the Tc 99m labeled mertiatide and free pertechnetate migrate to the solvent front.

A. Procedure Free Pertechnetate

1. Apply 1 drop of prepared Tc-99, mertiatide near the end of Whatman 3MM chromatography strip. Mark the point of sample application with a pencil line. Allow the spot to dry until the wet spot is no longer evident.

2. Develop the strip by ascending movement of Acetone.

3. Remove the test strip and mark the solvent front.

4. Allow strip to dry and place into a radiochromatogram scanner for determining the distribution of radioactivity. Note that free pertechnetate migrates to the solvent front.

OR

5. Cut strip midway between the point of sample application and the solvent front.

6. Count each section for activity using a gamma counter and subtract background.

7. Calculate the percent of free pertechnetate

$$\% \, TcO_2 = \frac{\text{cts upper section}}{\text{cts upper section + cts lower section}} \times 100$$

B. Procedure: Reduced-hydrolyzed Technetium (RHTc)

1. Apply a drop of prepared Tc 99m mertiatide to one end of a Whatman 3MM paper chromatography strip. The point of sample application should be marked with a pencil line. Allow the spot to dry until the water mark is no longer evident.

2. Develop the strip buy ascending movement of water.

3. Remove strip form solvent and mark solvent front.

4. Allow the strip to dry and determine the distribution of radioactivity on the strip by use of a radiochromatogram scanner. RHTc remains at the origin.

OR

5. Cut strip midway between the point of sample application and the solvent front.

6. Count each section using a gamma counter and subtract background.

7. Calculate the percent reduced-hydrolyzed Technetium:

$$\% \text{ RHTc} = \frac{\text{cts lower section}}{\text{cts lower section + cts upper section}} \times 100$$

The Tc 99m mertiatide is acceptable for use provided the sum of the free pertechnetate and RHTc do not exceed 10%.

- Use a 10 cm strip

RADIATION DOSIMETRY

The estimated absorbed radiation doses from an intravenous administration of technetium Tc 99m mertiatide are presented in Tables 4a and 4b.

Table 4a. Estimated Absorbed Radiation Doses for Technetium Tc 99m Mertiatide Injection in patients with Normal Renal Function (mGy) [5]

Subject	**Adult**	**15 yr**	**10 yr**	**5 yr**	**1 yr**
Administered Activity (MBq)	370	370	237	141	73
Organ	**Dose (mGy)**				
Adrenals	1.4E-01	1.9E-01	1.9E-01	1.7E-01	1.8E-01
Bladder	4.1E+01	5.2E+01	4.0E+01	2.5E+01	2.3E+01
Bone surfaces	4.8E-01	5.9E-01	5.0E-01	3.4E-01	3.1E-01
Brain	3.7E-02	4.8E-02	5.2E-02	4.9E-02	4.5E-02
Breast	3.7E-02	5.2E-02	5.7E-02	5.5E-02	6.0E-02
Gallbladder	2.1E-01	3.2E-01	4.7E-01	2.4E-01	2.0E-01
Stomach	1.4E-01	1.8E-01	2.3E-01	1.8E-01	1.8E-01
SI	8.5E-01	1.1E+00	1.0E+00	6.5E-01	5.7E-01
Colon	1.3E+00	1.6E+00	1.4E+00	8.5E-01	7.2E-01
ULI	6.3E-01	8.5E-01	8.1E-01	5.6E-01	4.9E-01
LLI	2.1E+00	2.6E+00	2.2E+00	1.2E+00	1.0E+00
Heart	6.7E-02	8.9E-02	8.8E-02	8.0E-02	8.8E-02
Kidneys	1.3E+00	1.6E+00	1.4E+00	1.2E+00	1.1E+00
Liver	1.1E-01	1.6E-01	1.8E-01	1.6E-01	1.5E-01
Lungs	5.6E-02	7.8E-02	7.8E-02	7.1E-02	7.3E-02
Muscles	5.2E-01	6.3E-01	5.2E-01	3.4E-01	3.0E-01
Oesophagus	4.8E-02	6.7E-02	6.6E-02	6.2E-02	6.0E-02
Ovaries	2.0E+00	2.6E+00	2.1E+00	1.2E+00	1.0E+00
Pancreas	1.5E-01	1.9E-01	2.2E-01	1.8E-01	1.8E-01
Red marrow	3.4E-01	4.4E-01	3.8E-01	2.1E-01	1.5E-01
Skin	1.7E-01	2.1E-01	2.0E-01	1.4E-01	1.3E-01

Subject	Adult	15 yr	10 yr	5 yr	1 yr
Administered Activity (MBq)	370	370	237	141	73
Organ	**Dose (mGy)**				
Spleen	1.3E-01	1.8E-01	1.9E-01	1.7E-01	1.7E-01
Testes	1.4E+00	2.0E+00	1.9E+00	1.2E+00	1.2E+00
Thymus	4.8E-02	6.7E-02	6.6E-02	6.2E-02	6.0E-02
Thyroid	4.8E-02	5.9E-02	6.4E-02	6.2E-02	6.0E-02
Uterus	4.4E+00	5.2E+00	4.5E+00	2.7E+00	2.3E+00
Remaining organs	4.8E-01	5.9E-01	5.0E-01	3.1E-01	2.6E-01
Effective dose (mSv)	**2.6E+00**	**3.3E+00**	**2.8E+00**	**1.7E+00**	**1.6E+00**

ULI = Upper large intestine; LLI = Lower large intestine

Table 4b. Estimated Absorbed Radiation Doses for Technetium Tc 99m Mertiatide Injection in patients with Normal Renal Function (rad) [5]

Subject	Adult	15 yr	10 yr	5 yr	1 yr
Administered Activity (mCi)	10	10	6.4	3.8	2.0
Organ	**Dose (rad)**				
Adrenals	1.4E-02	1.9E-02	1.9E-02	1.7E-02	1.8E-02
Bladder	4.1E+00	5.2E+00	4.0E+00	2.5E+00	2.3E+00
Bone surfaces	4.8E-02	5.9E-02	5.0E-02	3.4E-02	3.1E-02
Brain	3.7E-03	4.8E-03	5.2E-03	4.9E-03	4.5E-03
Breast	3.7E-03	5.2E-03	5.7E-03	5.5E-03	6.0E-03
Gallbladder	2.1E-02	3.2E-02	4.7E-02	2.4E-02	2.0E-02
Stomach	1.4E-02	1.8E-02	2.3E-02	1.8E-02	1.8E-02
SI	8.5E-02	1.1E-01	1.0E-01	6.5E-02	5.7E-02
Colon	1.3E-01	1.6E-01	1.4E-01	8.5E-02	7.2E-02
ULI	6.3E-02	8.5E-02	8.1E-02	5.6E-02	4.9E-02
LLI	2.1E-01	2.6E-01	2.2E-01	1.2E-01	1.0E-01
Heart	6.7E-03	8.9E-03	8.8E-03	8.0E-03	8.8E-03
Kidneys	1.3E-01	1.6E-01	1.4E-01	1.2E-01	1.1E-01
Liver	1.1E-02	1.6E-02	1.8E-02	1.6E-02	1.5E-02
Lungs	5.6E-03	7.8E-03	7.8E-03	7.1E-03	7.3E-03
Muscles	5.2E-02	6.3E-02	5.2E-02	3.4E-02	3.0E-02
Oesophagus	4.8E-03	6.7E-03	6.6E-03	6.2E-03	6.0E-03
Ovaries	2.0E-01	2.6E-01	2.1E-01	1.2E-01	1.0E-01
Pancreas	1.5E-02	1.9E-02	2.2E-02	1.8E-02	1.8E-02
Red marrow	3.4E-02	4.4E-02	3.8E-02	2.1E-02	1.5E-02

Subject	Adult	15 yr	10 yr	5 yr	1 yr
Administered Activity (mCi)	10	10	6.4	3.8	2.0
Organ	**Dose (rad)**				
Skin	1.7E-02	2.1E-02	2.0E-02	1.4E-02	1.3E-02
Spleen	1.3E-02	1.8E-02	1.9E-02	1.7E-02	1.7E-02
Testes	1.4E-01	2.0E-01	1.9E-01	1.2E-01	1.2E-01
Thymus	4.8E-03	6.7E-03	6.6E-03	6.2E-03	6.0E-03
Thyroid	4.8E-03	5.9E-03	6.4E-03	6.2E-03	6.0E-03
Uterus	4.4E-01	5.2E-01	4.5E-01	2.7E-01	2.3E-01
Remaining organs	4.8E-02	5.9E-02	5.0E-02	3.1E-02	2.6E-02
Effective dose (rem)	**2.6E-01**	**3.3E-01**	**2.8E-01**	**1.7E-01**	**1.6E-01**

ULI = Upper large intestine; LLI = Lower large intestine

Table 5. Fetal Absorbed Radiation Doses from a 10 mCi dose of Tc99m Mertiatide Injection[6]

Stage of Gestation	Fetal Dose mGy/MBq (rad/mCi)	Fetal Dose mGy (rad)
Early	0.018 (0.067)	6.7 (0.67)
3 months	0.013 (0.048)	4.8 (0.48)
6 months	0.0055 (0.020)	2.0 (0.20)
9 months	0.0052 (0.020)	1.9 (0.19)

OVERDOSAGE
No data available.

ACTION AND CLINICAL PHARMACOLOGY
Following intravenous injection of technetium Tc 99m mertiatide, the appearance, concentration, and excretion of the tracer in the kidney can be monitored to assess renal function. Although technetium Tc 99m mertiatide is highly plasma protein bound following intravenous injection, the protein binding is reversible and the tracer is rapidly excreted by the kidneys via active tubular secretion and glomerular filtration. Following intravenous injection of technetium Tc 99m mertiatide in normal volunteers, 89% of the tracer was plasma protein bound. In healthy subjects with normal renal function (mean serum creatinine 1.2 mg/dL), technetium Tc 99m mertiatide was rapidly cleared from the blood. The plasma clearance was approximately 0.3 liters/minute and the amount of technetium Tc 99m mertiatide excreted in the urine in three hours was nearly 90% of the dose. In a study performed in three patients with renal impairment (serum creatinine greater than 6.3 mg/dL), there was decreased blood clearance and a decrease in

the amount excreted in the urine over three hours. In these patients, 78% of the tracer was plasma protein bound after intravenous injection. The mean plasma clearance of technetium Tc 99m mertiatide was 0.03 liter/minute and 21.3% was excreted in three hours on average. In both healthy subjects and patients with renal impairment, the plasma concentration-time profile showed a biexponential decline.

Following intravenous administration, technetium Tc 99m mertiatide is actively concentrated in the kidney and urine of pediatric patients. Technetium Tc 99m mertiatide is excreted by the kidneys of pediatric patients in a pattern similar to that observed for adults. The cumulative urinary excretion of technetium Tc 99m mertiatide ranged from 63.9 to 80.0% at 90 minutes post-administration.

STORAGE AND STABILITY

Technescan MAG3™ should be stored at controlled room temperature (20-25°C, 68°-77°F) and protected from light until use. The reconstituted vial should be stored at controlled room temperature (20- 25°C, 68°-77°F) and must be used within six hours of preparation.

SPECIAL HANDLING INSTRUCTIONS

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 occupational workers.

This kit 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 regulations and/or appropriate licenses of local competent official organizations.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Catalog Number 096.

Technescan MAG3™ is supplied as a lyophilized powder packaged in vials. Each reaction vial contains 1 mg betiatide, 0.05 mg (minimum) stannous chloride dihydrate ($SnCl_2 \bullet 2H_2O$), 0.2 mg (maximum) total tin expressed as stannous chloride dihydrate ($SnCl_2 \bullet 2H_2O$), 40 mg sodium tartrate dihydrate ($Na_2C_4H_2O_6 \bullet 2H_2O$), and 20 mg lactose monohydrate.

The pH of the reconstituted drug is between 5.0 and 6.0. No bacteriostatic preservative is present.

Packages containing 5 reaction vials are available.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

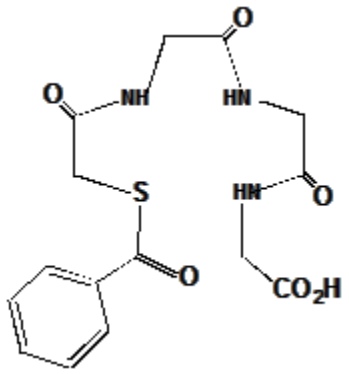
Drug Substance

Proper name: Betiatide

Chemical name: Not applicable

Molecular formula and molecular mass: Not applicable

Structural formula:



Physicochemical properties: Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.01 hours.

Product Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.01 hours[1].The principal photon that is useful for detection and imaging is listed in the table below.

Principal Radiation Emission Data[1]

Radiation	Mean % per Disintegration	Energy (keV)
Gamma-2	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 thickness of lead (Pb) for Technetium Tc 99m is 0.023cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in the following table. For example, the use of 0.27 cm of Pb will decrease the external radiation exposure by a factor of about 1000.

Radiation Attenuation by Lead Shielding[2]

Shield Thickness Pb, (cm)	Coefficient of Attenuation
0.023	0.5
0.09	10^{-1}
0.18	10^{-2}
0.27	10^{-3}

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

Physical Decay Chart: Technetium Tc 99m; Half-Life 6.01 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.780	10	0.316
-4	1.586	11	0.281
-3	1.413	12	0.251
-2	1.259	13	0.223
-1	1.122	14	0.199
0*	1.000	15	0.177
1	0.891	16	0.158
2	0.794	17	0.141
3	0.708	18	0.125
4	0.631	19	0.112
5	0.562	20	0.100
6	0.501	21	0.0888
7	0.446	22	0.0791
8	0.398	23	0.0705
9	0.354	24	0.0628

* Calibration Time

CLINICAL TRIALS

No data available.

DETAILED PHARMACOLOGY

The biodistribution and distribution patterns of technetium Tc 99m mertiatide was examined in laboratory mice and rats. In all species examined, intravenously administered technetium Tc 99m mertiatide was extensively bound to plasma protein which inhibited extravascular distribution. The protein bound technetium Tc 99m mertiatide is rapidly concentrated by tubular secretion and excreted in the urine. The non-plasma bound fraction of technetium Tc 99m mertiatide is excreted by glomerular filtration.

Similar biodistribution and excretion patterns were observed in human studies.

The use of technetium Tc 99m mertiatide as a renal imaging agent is based on its clearance through the urinary tract predominantly by active tubular secretion in the proximal renal tubules, and to a lesser extent by glomerular filtration. In the presence of renal artery ligation in animals, excretion of technetium Tc 99m mertiatide shifts to secretion by the liver. This shift to hepatic excretion has been observed to a lesser extent in patients with severe renal dysfunction.

TOXICOLOGY

The acute toxicity of technetium Tc 99m mertiatide was examined in mice and rabbits following a single intravenous injection of technetium Tc 99m mertiatide followed by a 7-day observation period. There were no adverse effects observed in animals receiving up to 1000x (mice) and 100x (rabbits) the maximum intended human clinical dose.

The subacute toxicity of technetium Tc 99m mertiatide was evaluated in rats and rabbits following 14 daily intravenous injections. There were no adverse effects observed in animals at doses up to 30x the maximum intended clinical dose.

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

REFERENCES

1. Stabin MG, da Luz CQPL. Decay Data for Internal and External Dose Assessment, Health Phys. 83(4):471-475, 2002.

2. Smith David S., Stabin, Michael G. Exposure Rate Constants and Lead Shielding Values for Over 1,100 Radionuclides, Health Physics. 102(3):271-291, March 2012.

3. Oei HY, Chapter 23, "Dynamic and Static Renal Imaging," in Nuclear Medicine in Clinical Diagnosis and Treatment, Vol 1, pp. 213-227, Murray IPC and Ell PJ, Churchill, Livingstone, 1994, London

4. Brown SCW, Chapter 28, "Nuclear Medicine in the Clinical Diagnosis and Treatment of Obstructive Uropathy," in Nuclear Medicine in Clinical Diagnosis and Treatment, Volume 1, pp. 271 - 274, ed. by Murray IPC and Ell PJ, Churchill Livingstone, London, 1994.

5. International Commission on Radiological Protection. ICRP Publication 80, Radiation Dose to Patients from Radiopharmaceuticals: Addendum 2 to ICRP Publication 53, Ann. ICRP 28(3), 1998.

6. Russell JR and Stabin MG, Sparks RB and Watson EE. Radiation Absorbed Dose to the Embryo/Fetus from Radiopharmaceuticals. Health Phys 73(5):756-769, 1997

PART III: CONSUMER INFORMATION

TechnescanMAG3™
Kit for the Preparation of Technetium Tc 99m Mertiatide

This leaflet is part III of a three-part "Product Monograph" published when Technescan MAG3™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Technescan MAG3™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Technescan MAG3™ is used to diagnose kidney abnormalities, kidney failure, urinary tract obstructions, and kidney stones in adults and children.

Technescan MAG3™ is also used to test kidney blood flow and function, as well to image kidney size, position, and blood vessels. This medication is also used for kidney studies called renograms.

What it does:
Technescan MAG3™ is a radioactive tracer that is injected into a vein, then travels through the body and out through the kidneys and urinary tract. After injection of the tracer, pictures of the kidneys and urinary tract can be taken with a special camera.

What the medicinal ingredient is:
Betiatide

What the important non-medicinal ingredients are:
Lactose monohydrate, stannous chloride dihydrate, sodium tartrate dihydrate and total tin expressed as stannous chloride.

For a full listing of non-medicinal ingredients see Part 1 of the product monograph.

WARNINGS AND PRECAUTIONS

Since Technescan MAG3 ™ is a radiopharmaceutical, it can only be given by a healthcare professional who is specially trained and experienced 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.

BEFORE you receive Technescan MAG3 ™ talk to your doctor or pharmacist if:

- You had any allergic reaction to this radiopharmaceutical in the past or its ingredients.
- There is a possibility that you may be pregnant. If there is a need to consider Technescan MAG3™ during your pregnancy, your doctor will discuss the benefits and risks of giving it to you.
- You are breastfeeding your baby. Technetium Tc 99m is excreted in human milk during lactation; therefore, formula feedings should be substituted for breastfeeding for at least 24 hours after administration of Technescan MAG3™.

Drink fluids and use the toilet as often as possible after receiving an injection of Technescan MAG3™ for six hours to reduce the amount of radiation your bladder and other organs are exposed to.

Safety precautions to be followed for up to 12 hours after receiving Technescan MAG3™:

- Men should use toilet instead of urinal.
- Toilet should be flushed several times after use.
- Wash hands thoroughly after using toilet.

If you have difficulty with bladder control, special precautions may be used to minimize the risk of radioactive contamination of clothing, bed linen and your surroundings.

INTERACTIONS WITH THIS MEDICATION

No interactions are known, however, your doctor should be informed about all the prescribed or over-the-counter products you use.

PROPER USE OF THIS MEDICATION

Technescan MAG3™ will be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Possible side effects may include nausea, vomiting, wheezing, difficulty breathing, itching, skin rash, rapid heartbeat, high blood pressure, shaking chills, fever, and seizure. Should you experience any side effect following the administration of Technescan MAG3™, be sure to tell your doctor.

This is not a complete list of side effects. If you have any unexpected effects after receiving Technescan MAG3™, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

•Report online at www.healthcanada.gc.ca/medeffect
•Call toll-free at 1-866-234-2345
•Complete a Canada Vigilance Reporting Form and:

- **Fax toll-free to 1-866-678-6789, or**
- **Mail to: Canada Vigilance Program**
  Health Canada
  Postal Locator 1908C
  Ottawa, ON K1A 0K9

You can also report suspected adverse reactions directly to Curium Canada Inc. by one of the following 2 ways:

- **Call toll-free at 1-866-789-2211**
- **Mail to: Curium Canada Inc.**
  c/o Pharmacovigilance Department
  2572 Boul. Daniel-Johnson, Suite 248
  Laval, Quebec, H7T-2R3

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Curium Canada Inc. at 1-866-885-5988.

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