AUSTRALIAN PRODUCT INFORMATION

TECHNESCAN MAG3™ (BETIATIDE) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

Betiatide.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Technescan MAG3™ is a kit for the preparation of Technetium Tc 99m Mertiatide, a diagnostic radiopharmaceutical agent.

Technescan MAG3 is supplied as a sterile, non-pyrogenic, lyophilised powder, packaged under argon. 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 when formed is suitable for intravenous administration.

Each vial contains 1 mg betiatide. The pH of the reconstituted drug is between 5.0 and 6.0. No bacteriostatic preservative is present. Betiatide is light sensitive and must be protected from light.

For the full list of excipients, see Section **6.1 LIST OF EXCIPIENTS**.

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 is listed in **Table 1**.

Table 1. Principal Radiation Emission Data[1]

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

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

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 0.017 cm. 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 0.25 cm of Pb will decrease the external radiation exposure by a factor of about 1000.

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 the 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(^{99m}Tc), Half-life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

*Calibration Time

3 PHARMACEUTICAL FORM

Powder for Injection.

Technescan MAG3 is a white lyophilised powder in a glass vial intended for intravenous injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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 paediatric patients (see Section **4.4 - Paediatric use**). It is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The suggested dose range employed in the average adult patient (70 kg) for renal function and imaging studies is 185 megabecquerel (MBq) (5 millicurie [mCi]) to 370 MBq (10 mCi).

In paediatric patients the recommended dose range is 2.6 MBq/kg (70 μCi/kg) to 5.2 MBq/kg (140 μCi/kg) with a minimum dose of 37 MBq (1 mCi).

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

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

Aseptic procedures and a shielded syringe should be employed in withdrawing doses for administration to patients. The user should wear waterproof gloves during the administration procedure.

Radiation Dosimetry

The estimated absorbed radiation doses from an intravenous administration of Technetium Tc 99m Mertiatide are presented in **Table 4**.

Table 4. Estimated Absorbed Radiation Doses

Ages	**8 day old**		**1 year old****		**5 year old****		**10 year old****		**15 year old**		**Adult**	
Assumed Weight (kg)	3.4		9.8		19		32		57		70	
Tc 99m **Mertiatide Dose**	37 MBq (1 mCi)		72.52 MBq (1.96 mCi)		140.6 MBq (3.8 mCi)		236.8 MBq (6.4 mCi)		370 MBq (10 mCi)		370 MBq (10 mCi)	
Organ	mSv	rem	mSv	rem	mSv	rem	mSv	rem	mSv	rem	mSv	rem
Gallbladder Wall	2.701	0.27	2.466	0.235	1.547	0.160	1.658	0.166	1.961	0.200	1.628	0.160
Lower Large Intestine Wall	1.739	0.17	1.595	0.161	2.250	0.220	2.368	0.237	4.070	0.400	3.256	0.330
Small Intestine	0.518	0.052	0.5439	0.055	1.195	0.122	1.397	0.141	2.035	0.200	1.628	0.160
Upper Large Intestine Wall	0.962	0.096	0.943	0.096	1.828	0.186	2.0365	0.205	2.442	0.250	1.887	0.190
Kidneys	1.406	0.14	1.088	0.112	1.308	0.129	1.5155	0.154	1.739	0.180	1.443	0.140
Liver	0.3219	0.032	0.3046	0.031	0.394	0.038	0.4262	0.0435	0.481	0.048	0.3626	0.036
Ovaries	0.592	0.058	0.6164	0.061	1.322	0.133	1.5392	0.154	3.330	0.330	2.5900	0.260
Red Marrow	0.1628	0.016	0.1595	0.161	0.281	0.0277	0.3552	0.0352	0.629	0.063	0.4810	0.050
Testes	0.518	0.051	0.5294	0.053	1.0826	0.110	1.1840	0.122	2.368	0.240	1.628	0.160
Unitary Bladder Wall	11.470	1.1	9.428	0.921	21.090	2.090	23.680	2.368	29.20	6.00	48.1000	4.80
Total Body	0.2405	0.024	0.2176	0.022	0.3656	0.0365	0.4026	0.0410	0.814	0.081	0.6660	0.065

millisievert (mSv); roentgen (rem)

* Calculated by Oak Ridge Associated Universities, based upon the paediatric phantom series of Christy and Eckerman of Oak Ridge National Laboratories. The adult radiation absorbed doses were calculated based on data from ten normal volunteers using the Medical Internal Radiation Dose Committee (MIRD) schema.

** Radioactive doses for 1, 5, and 10 year olds are based on a maximum dose of 7.4 MBq/kg (200 μCi/kg).

Preparation of Technetium Tc 99m Mertiatide

Note: Read complete directions thoroughly before starting preparation procedure.

Procedural Precautions and Notes

1. Solutions of Sodium Pertechnetate Tc 99m which contain oxidising agents (i.e. sodium hypochlorite or hydrogen peroxide) should not be used.
   Note: Do not use Tc 99m
   eluate more than 6 hours after its elution from the generator.

2. All transfers and vial stopper entries must be done using aseptic technique.

3. 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 water of the bath, and the level of the bath must be at least even with the level of the contents of the vial.

4. 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: 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 solution during the preparation procedure with an adequately shielded syringe.

Note 3: Keep the radioactive preparation in the lead shield described below (with cap in place) during the useful life of the radioactive preparation. Maintain adequate shielding during the life of the product and use a shielded, sterile syringe for withdrawing and injecting the preparation.

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 (one eighth) 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 gigabecquerels (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 Sodium Pertechnetate Tc 99m to the reaction vial.

4. Immediately following the addition of Sodium Pertechnetate Tc99m 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 oxidise excess stannous ion. Remove both needles from the vial.
   Note: The addition of 2 mL air is required to prevent the progressive formation of Technetium Tc99m labelled 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 Tc99m solution.

7. Remove the reaction vial from the boiling water bath and place 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 Tc99m 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 Tc99m Mertiatide below 30°C and protect from light until use. The Technetium Tc99m Mertiatide preparation must be used within 6 (six) hours of preparation.

Method of Administration

Required Materials:

Waters Sep-Pak® C18 Cartridges, Part #51910, 200 proof ethanol

0.9% Sodium Chloride Injection, USP 0.001N hydrochloric acid*

1:1 ethanol/saline solution**

Disposable syringes:

10 mL, no needle required

1 mL, with needle

Disposable culture tubes or vials, minimum 15 mL capacity

Ion chamber for measurement of radioactive samples.

*May be prepared by diluting 1 mL of 0.10N 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% (~11.6N) 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 0.001N 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 Tc99m 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 drop-wise 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-hydrolysed technetium.

2. Assay the activity of the second elution. This fraction contains the Technetium Tc99m Mertiatide complex.

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

Calculations

1. Percent Technetium Tc99m Mertiatide =

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

2. Percent hydrophilic impurities =

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

3. Percent non-elutable impurities =

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

This reagent kit is approved for distribution to persons licensed by the U.S. Nuclear Regulatory Commission to use byproduct material identified in Section 35.200 or under an equivalent license of an Agreement State.

4.3 CONTRAINDICATIONS

None known.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The contents of this kit are not radioactive. However, after Sodium Pertechnetate Tc99m is added, adequate shielding of the final preparation must be maintained.

Contents of the reaction vial are intended only for use in the preparation of Technetium Tc99m Mertiatide and are NOT to be administered directly to the patient.

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 Tc99m Mertiatide for six (6) hours after the imaging procedure.

Technetium Tc99m Mertiatide should not be used more than six (6) hours after preparation.

The components of the kit are sterile and non-pyrogenic. It is essential that the user follow the directions carefully and use 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.

The Technetium Tc99m labelling reactions involved in preparing Technescan MAG3 depend on maintaining the stannous ion in the reduced state. Any oxidant present in the Sodium Pertechnetate Tc99m may adversely affect the quality of the radiopharmaceutical, therefore, Sodium Pertechnetate Tc99m containing oxidants should not be employed.

As in the use of any other radioactive material, care should be taken to ensure minimum radiation exposure to the patient and to occupational workers.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides.

Use in the elderly

There is no special safety or dosage information available for use in the elderly.

Paediatric use

Safety and effectiveness in paediatric patients under the age of 30 days have not been established.

Effects on laboratory test

This information is not available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

This information is not available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No long term animal studies have been performed to evaluate carcinogenic or mutagenic potential, or whether this drug affects fertility in males or females.

Use in pregnancy

Animal reproduction studies have not been conducted with Technetium Tc99m Mertiatide. It is also not known whether this medicine can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Technetium Tc99m Mertiatide should be given to a pregnant woman only if clearly needed.

Use in lactation

Technetium Tc 99m is excreted in human milk during lactation. Therefore, formula feedings should be substituted for breast feeding.

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)

Body as a Whole: shaking, chills, fever.

Cardiovascular: tachycardia, hypertension.

Digestive: nausea, vomiting.

Nervous System: seizure.

Respiratory System: wheezing, dyspnoea.

Skin and Appendages: itching, rash.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The risk of an excessive Technetium Tc99m Mertiatide dose is largely theoretical and most likely to be due to excessive radiation exposure. In such circumstances the radiation to the body (kidney, bladder and gallbladder) can be reduced by forced diuresis and frequent bladder voiding.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

This information is not available.

Clinical trials

No data available.

5.2 PHARMACOKINETICS PROPERTIES

Absorption

In both healthy subjects and patients with renal impairment, the plasma concentration- time profile showed a biexponential decline.

Distribution

Following intravenous injection of Technetium Tc99m Mertiatide, the appearance, concentration, and excretion of the tracer in the kidney can be monitored to assess renal function. Following intravenous injection of Technetium Tc99m 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 Tc99m Mertiatide was rapidly cleared from the blood. The plasma clearance was approximately 0.3 liters/minute and the amount of Technetium Tc99m Mertiatide excreted in the urine in three hours was nearly 90% of the dose.

Metabolism

This information is not available.

Excretion

Although Technetium Tc99m 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.

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 Tc99m Mertiatide was 0.03 liters/minute and 21.3% was excreted in three hours on average.

5.3 PRECLINICAL SAFETY DATA

No long term animal studies have been performed to evaluate carcinogenic or mutagenic potential, or whether Tc99m-labelled Technetium MAG3 (Technetium Tc99m Mertiatide) affects fertility in males or females.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate

Sodium tartrate dihydrate

Stannous chloride dihydrate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Before reconstitution: 12 months from date of manufacture.

After reconstitution: must be used within six (6) hours of preparation.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Before reconstitution: Store between 15 to 25ºC. Protect from light until use.

After reconstitution: Store between 15 to 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Glass vial.

Packs contain 5 vials.

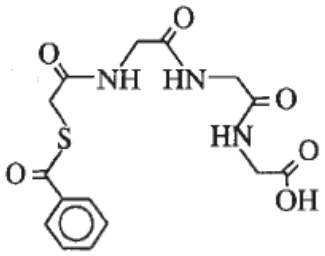
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

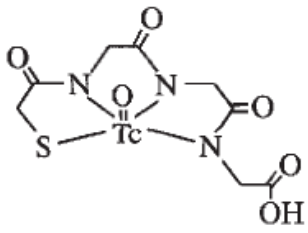
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Betiatide and Technetium Tc99m Mertiatide have the following structural formulas:



betiatide



technetium (^{99m}Tc) mertiatide

CAS number

CAS number for betiatide: 103725-47-9.

CAS number for Technetium Tc99m Mertiatide: 125224-05-7.

7 MEDICINE SCHEDULE

Not scheduled. Not considered by committee.

8 SPONSOR

Landauer Radiopharmaceuticals Pty Ltd

Level 3/69 Phillip Street

Parramatta NSW 2150

Australia

Contact Number: (02) 8651 4000

9 DATE OF FIRST APPROVAL

12 June 1991

10 DATE OF REVISION

13 January 2020

Revision Date: R01/2020
Made in the USA

CURIUM™

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Summary Table of Changes

Section changed	Summary of new information
All sections	Adopted new TGA approved PI form throughout the document with no change to previously approved TGA text. New text added were necessary to comply with the new PI form.