SUMMARY OF PRODUCT CHARACTERISTICS

FROSSTIMAGE/DRAXIMAGE KIT FOR THE PREPARATION OF TC99M (DTPA)

For Intravenous Use,

Solution for Injection containing

Calcium Trisodium Pentetate 20 mg/vial

1 INDICATIONS

Kidney, brain, aerosol imaging.

Technetium Tc 99m Pentetate Injection may be used to perform kidney imaging and brain imaging, to assess renal perfusion and to estimate glomerular filtration rate.

Technetium Tc 99m pentetate, administered by inhalation following nebulization to aradio- aerosol, may be used to perform lung ventilation studies as an aid in the assessment of pulmonary embolic or obstructive airway disease.

2 CONTRAINDICATIONS

Technetium Tc 99m Pentetate is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing (See *6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)*.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

DTPA should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Intravenous Administration

The image quality may be adversely affected by impaired renal function.

Literature reports indicate that the target to non-target ratio for intracranial lesions may take several hours to fully develop and the possibility of missing certain lesions by restricting imaging to the early period after injection should be kept in mind.

Inhalation Administration

The instructions accompanying the aerosol delivery system must be followed in order to ensure proper delivery of the radio-aerosol to the lungs. It may be useful to have the patient breathe nebulized isotonic saline for practice, prior to the administration of the radiopharmaceutical. A

typical time period for inhalation of the radio-aerosol for lung ventilation studies is 2 to 4 minutes. At the end of the study, the patient should be instructed to rinse their mouth and expectorate into a disposable container.

4.2 Recommended Dose and Dosage Adjustment

Health Canada has not authorized an indication for pediatric use.

Dosage for Intravenous Administration:

The recommended dose range for intravenous administration to the average patient (70 kg) after reconstitution with oxidant-free sodium pertechnetate Tc 99m is provided in Table 1.

Table 1. Technetium Tc 99m Pentetate solution – Intravenous Injection

Indication	Dose
Kidney Imaging and Glomerular Filtration Rate Estimation	111 MBq to 185 MBq (3 mCi to 5 mCi)
Brain Imaging	370 MBq to 740 MBq (10 mCi to 20 mCi)
Renal Imaging and Perfusion Assessment	370 MBq to 740 MBq (10 mCi to 20 mCi)

Dosage for Inhalation Administration

Table 2. Technetium Tc 99m Pentetate solution – Aerosol Inhalation Administration

Indication	Dose
Lung Ventilation	370 MBq to 1670 MBq (10 mCi to 45 mCi)

4.3 Reconstitution

Reaction vials containing the sterile, non-pyrogenic, lyophilized powder are reconstituted with 2 to 10 mL of technetium Tc 99m to prepare Technetium Tc 99m Pentetate Injection for intravenous and inhalation administration. (See *11 STORAGE, STABLITY and DISPOSAL)*

4.4 Administration

See *4.7 Instructions for Preparation and Use* for the preparation of Tc 99m labelled DTPA.

- Using proper shielding, visually inspect the Tc 99m labelled DTPA Injection after reconstitution for particulate matter and discoloration prior to administration. Do not use or administer if there is evidence of foreign matter or the solution is not clear.
- Measure the patient dose by a radioactivity calibration system immediately prior to administration. Withdrawal for administration must be made aseptically.

<u>Intravenous Use</u>

- Instruct the patient to increase fluid intake and to void frequently for the next 4 to 6 hours after Tc 99m labelled DTPA administration by injection to minimize the radiation dose to the bladder.

Inhalation Use

- Use the selected nebulizer in accordance with the manufacturer's instructions.
- Instruct the patient to rinse their mouth and expectorate after Tc 99m labelled DTPA administration by inhalation to minimize the radiation dose to the mouth and esophagus.

4.6 Image Acquisition and Interpretation

For lung ventilation studies, there may be deposition of particles in proximal airways influencing image quality and interfering with diagnostic interpretation in patients with obstructive pulmonary disease. (See *7 WARNINGS AND PRECAUTIONS)*

Post administration of the dosage the Image acquisition is completed as per the information provided in **Table 3** and **Table 4**.

Table 3. Technetium Tc 99m Pentetate solution – Intravenous Injection

Indication	Route of Administration	Image Acquisition
Brain Imaging	Intravenous Injection	Immediate dynamic imaging (flow). Obtain at least one blood-pool image in same position as flow. Delayed images can be obtained 1 hour later.
Renal Imaging and Perfusion Assessment	Intravenous Injection	Immediate dynamic imaging (flow). Static imaging 1 to 30 minutes after injection.
Renal imaging with Estimation of Glomerular Filtration Rate	Intravenous Injection	Immediate dynamic imaging (flow). Static imaging 1 to 30 minutes after injection.

Table 4 Technetium Tc 99m Pentetate solution – Aerosol Inhalation Administration

Indication	Route of Administration	Image Acquisition
Lung Ventilation	Aerosol Inhalation	For lung imaging performed prior to perfusion imaging, the target administered dose to the lungs is achieved after 3 to 5 minutes of inhalation or at an imaging count rate of 50,000 to 100,000 per minute*.

* For lung imaging performed after perfusion imaging, target count rate should be approximately three times that of perfusion count rate.

4.7 Instructions for Preparation and Use

The preparation of Technetium Tc 99m Pentetate Injection may be accomplished by the following procedure.

- Waterproof gloves are to be worn during the preparation and elution processes;
- Aseptic techniques should be employed throughout the preparation and elution processes.
- Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial during the useful life of the radioactive product.

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.

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.

Intravenous Administration

To prepare Technetium Tc 99m Pentetate 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 which has a fitted lead cap. Obtain 2 to 10 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 18.5 GBq (500 mCi). Sodium pertechnetate Tc 99m solutions containing an oxidizing agent are not suitable for use.
3. Using a shielded syringe, aseptically add the sodium pertechnetate Tc 99m solution to the reaction vial, while avoiding the buildup of excessive pressure in the vial. Pressure buildup may be avoided by injecting several millilitres of pertechnetate solution into the reaction vial, then withdrawing several millilitres of nitrogen gas (present to prevent oxidation of the complex) into the syringe. Repeat the procedure as necessary until the entire amount of pertechnetate is added to the vial and normal pressure is established within the vial.

4. Place the lead cap on the vial shield and gently agitate the shielded vial until the contents are completely dissolved. To ensure maximum radiolabelling, allow the preparation to stand for 5 to 15 minutes at room temperature (15 °C to 30 °C). Using proper shielding, the reaction vial should be visually inspected to ensure that the solution is clear and free of particulate matter before proceeding; if it is not, the radiopharmaceutical should not be used.
5. Assay the product in a suitable calibrator, record the radioassay information, date and time on the label with radiation warning symbol. Apply the label to the lead vial shield.
6. The radiochemical purity of the finished preparation should be determined prior to patient administration. The radiochemial purity should not be less than 90%.
7. Withdrawals for administration must be made aseptically using a sterile needle and syringe. Since the vials contain nitrogen, the vials should not be vented. If repeated withdrawals are made, the replacement of the contents from the vial with air should be minimized.
8. The finished preparation should be discarded 12 hours after reconstitution. While radioactive, it should be retained in a lead vial shield with the lead cap in place.

Inhalation Administration

To prepare Technetium Tc 99m Pentetate for inhalation with an aerosol delivery system, follow the directions detailed above (*Intravenous Administration*), keeping in mind the requirements of specific activity necessitated by the nebulizer to be used and follow the nebulizer manufacturer's instructions for nebulization and administration of radio-aerosol.

Directions for Quality Control

Radiochemical Purity

Chromatographic Methods

The following procedure describes a series of simple steps for running chromatograms. Step 5 describes two methods, one for determining free pertechnetate in a mixture of chelated and reduced technetium and the other for determining reduced technetium in a mixture of chelated technetium and pertechnetate. The TLC procedure requires the following:

Solid Phase: ITLC-SG

Solvant A: 0.9% Sodium Chloride (for determination of reduced technetium)

Solvant B: 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 microlitre disposable micropipette (e.g. Fisher Scientific 21-164-2D) 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.

In the saline system, reduced $^{99m}TcO_2$ stays at the origin (R_f 0), while the bound and free technetium $^{99m}TcO_4^-$ move to the front of R_f 0.85 to 1.0.

In the acetone system, the bound and reduced fractions stay at the origin while free pertechnetate $^{99m}TcO_4^-$ migrates to the front R_f 0.85 to 1.0.

Step 5

Method A - Determination of reduced technetium, using saline solvent:

Cut the dried strip 3 cm from the origin. The short piece is marked as *Part I* and the long piece is marked as *Part II*. Count the pieces in a suitable counter and determine the percentage of reduced technetium according to the following formula:

$$\text{Percent } ^{99m}TcO_2 = \frac{\text{Counts in } \textit{Part I}}{\text{Counts in } \textit{Part I} + \textit{Part II}} \times 100$$

Method B - Determination of pertechnetate using acetone:

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

$$\text{Percent } ^{99m}TcO_4^- = \frac{\text{Counts in } \textit{Part IV}}{\text{Counts in } \textit{Part III} + \textit{Part IV}} \times 100$$

NOTE: IT IS IMPORTANT TO NOTE THAT THE STRIPS ARE CUT IN DIFFERENT POSITIONS FOR METHODS A AND B.

Step 6

Determine the amount of bound technetium according to the following formula:

Percent chelated $^{99m}Tc = 100 - \% \ ^{99m}TcO_4^- - \% \ ^{99m}TcO_2$

Step 7

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

4.8 Radiation Dosimetry

The estimated radiation absorbed dose to various organs from an intravenous injection of Tc 99m pentetate in patients with normal and abnormal renal function is shown respectively in Table 5 and Table 6.

Table 5. Estimated Radiation Absorbed Dose for Technetium Tc 99m Pentetate Injection in Patients with Normal Renal Function Following Intravenous Injection

Absorbed Dose Per Unit Activity Administered (mcGy/MBq)	
Organ	**Adult**
Adrenals	1.4
Bone surfaces	2.4
Brain	0.86
Breast	0.72
Gallbladder wall	1.5
Gastrointestinal tract	
Esophagus	1.0
Stomach wall	1.3
Small intestine wall	2.5
Colon wall	3.1
Upper large intestine wall	2.1
Lower large intestine wall	4.3
Heart wall	1.2
Kidneys	4.4
Liver	1.2
Lungs	1.0
Muscles	1.6
Ovaries	4.2

Absorbed Dose Per Unit Activity Administered (mcGy/MBq)	
Organ	**Adult**
Pancreas	1.4
Red marrow	1.5
Skin	0.87
Spleen	1.3
Testes	2.9

Thymus	1.0
Thyroid	1.0
Urinary bladder wall	62
Uterus	7.9
Remaining organs	1.7
Effective dose per unit activity (mcSv/MBq)	**4.9**

Table 6. Estimated Radiation Absorbed Dose for Technetium Tc 99m Pentetate Injection in Patients with Abnormal Renal Function Following Intravenous Injection

Absorbed Dose Per Unit Activity Administered (mcGy/MBq)	
Organ	**Adult**
Adrenals	4.1
Bone surfaces	6.0
Brain	2.8
Breast	2.3
Gallbladder wall	4.2
Gastrointestinal tract	
Esophagus	3.3
Stomach wall	3.8
Small intestine wall	4.5
Colon wall	4.5
Upper large intestine wall	4.3
Lower large intestine wall	4.9
Heart wall	3.7
Kidneys	7.7
Liver	3.7
Lungs	3.3
Muscles	3.2
Ovaries	5.0
Pancreas	4.3
Red marrow	3.4

Absorbed Dose Per Unit Activity Administered (mcGy/MBq)	
Organ	**Adult**
Skin	2.2
Spleen	3.8
Testes	3.5
Thymus	3.3
Thyroid	3.4
Urinary bladder wall	21
Uterus	6.1
Remaining organs	3.3
Effective dose per unit activity (mcSv/MBq)	**4.6**

The estimated radiation absorbed dose to various organs from the inhalation of Tc 99m Pentetate Injection is shown in Table 7.

Table 7. Estimated Radiation Absorbed Dose for Technetium Tc 99m Pentetate Injection Administered by Inhalation

Absorbed Dose Per Unit Activity Administered (mcGy/MBq)	
Organ	**Adult**
Adrenals	2.1
Bone surfaces	1.9
Breast	1.9
Gastrointestinal tract	
Stomach wall	1.7
Small intestine wall	2.1
Upper large intestine wall	1.9
Lower large intestine wall	3.2
Kidneys	4.1
Liver	1.9
Lungs	17
Ovaries	3.3
Pancreas	2.1
Red marrow	2.7
Spleen	1.9
Testes	2.1
Thyroid	0.99
Urinary bladder wall	47
Uterus	5.9
Other tissue	1.8
Effective dose per unit activity (mcSv/MBq)	**5.9**

5 OVERDOSAGE

In the event of the administration of a radiation overdose, if the patient's medical condition allows, the absorbed dose should be reduced where possible by increasing the elimination of the radionuclide from the body via forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective dose that was applied.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

DTPA (Kit for the preparation of Technetium Tc 99m Pentetate Injection) is available in cartons containing 10 reaction vials, each reaction vial containing, in lyophilized form, sterile and non-pyrogenic:

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous and Inhalation	Powder for Solution 20.0 mg/vial Pentetic Acid, USP	para-Aminobenzoic Acid - 5.0 mg, Calcium Chloride Dihydrate - 3.73 mg, Stannous Chloride Dihydrate - 0.35 mg

The pH is adjusted with HCl and/or NaOH prior to lyophilization. The pH of the reconstituted radiopharmaceutical is 6.5 to 7.5. The vials are sealed under an atmosphere of nitrogen.

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

6.1 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies is listed in Table 8.

Table 8. Principal Radiation Emission Data

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

6.2 External Radiation

The specific gamma ray constant for technetium Tc 99m is 5.44 mcC•kg^{-1}•MBq^{-1}•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 1000. A range of values for the relative attenuation of the radiation resulting from the interposition of various thicknesses of lead is shown in Table 9.

Table 9. 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 10.

Table 10. 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

* Calibration Time

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

The product should be administered under the supervision of a health professional 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 radiopharmaceutical product 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.

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.

The contents of the reaction vial are intended **ONLY** for use in the preparation of Technetium Tc 99m Pentetate Injection and are **NOT** to be administered directly to the patient.

The contents of the reaction vial before preparation 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.

The technetium Tc 99m labelling reactions involved in preparing the agent depend on

maintaining the stannous ion in the reduced state. Any oxidant present in the sodium pertechnetate Tc 99m solution may thus adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc 99m solutions containing oxidants should not be employed.

The components of the kit are supplied sterile and non-pyrogenic (preservative-free). Aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during the addition of the sodium pertechnetate Tc 99m solution and the withdrawal of doses for patient administration.

After labelling with technetium Tc 99m, the solution may be stored at cool temperature (2 °C to 8 °C) in a suitable lead shield.

DTPA is **not** formulated for intrathecal administration.

Carcinogenesis and Mutagenesis

No long term animal studies have been performed to evaluate carcinogenic potential of Technetium Tc 99m Pentetate Injection. Mutagenesis studies have not been conducted.

Immune

Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, have been reported during post-approval diagnostic use of Technetium Tc 99m Pentetate Injection. Monitor all patients for hypersensitivity reactions and have access to cardiopulmonary resuscitation equipment and personnel.

Radiation Exposure

Technetium Tc 99m contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure. Use the lowest dose of Technetium Tc 99m Pentetate necessary for imaging. Encourage patients to drink fluids and bladder void as frequently as possible after intravenous administration. Instruct the patient to rinse their mouth and expectorate after inhalation administration. (See *4.4 Administration)*

Reproductive Health: Female and Male Potential

Studies have not been performed to evaluate whether Technetium Tc 99m Pentetate Injection has an effect on fertility in males or females. (See *7.1.1 Pregnant Women)*

Respiratory

As with other inhaled medications, inhalation of Technetium Tc 99m Pentetate solution may result in acute bronchoconstriction, especially in patients with heightened bronchoreactivity, such as patients with asthma or other lung or allergic disorders. Monitor all patients for

bronchoconstriction.

Risks for Image Misinterpretation

In patients with obstructive pulmonary disease there may be deposition of particles in the proximal airways influencing image quality and interfering with diagnostic interpretatio n, therefore to ensure diagnostic quality, careful use of the nebulizer to assure optimal particle delivery is essential. If interfering particle deposition occurs, consider additional diagnostic options.

7.1 Special Populations

7.1.1 Pregnant Women

No animal reproductive studies have been conducted with technetium Tc 99m pentetate.

It is not known whether Technetium Tc 99m Pentetate Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have bee n no studies in pregnant women. Technetium Tc 99m Pentetate Injection should be given to a pregnant woman only if clearly needed.

All radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering Technetium Tc 99m Pentetate administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from technetium Tc 99m pentetate and the gestational timing of exposure.

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 or after ensuring the woman is not pregnant. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

7.1.2 Breast-feeding

Free Technetium Tc 99m is excreted in human milk during lactation. Mothers may nurse the infant just before administration of technetium 99m pentetate. If required, formula feedings could be substituted for breast feedings for at least 6 hours following the administration of the product. After expressing the milk completely and discarding it during that period of time, breastfeeding may resume.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available; therefore, it has not been authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No formal studies of technetium Tc 99m pentetate in the

elderly were performed to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

Most common adverse reactions reported post-market in patients receiving Technetium Tc 99m Pentetate injection include; allergic reactions, rash, itching.

See Sensitivity reactions under section *7 WARNINGS AND PRECAUTIONS.*

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified post-approval, from Canadian and international exposure. Because these reactions are voluntarily reported from a population of uncertain size, it is not always possible to reliably estimate their exact frequency or establish a causal relationship to Technetium Tc 99m Pentetate exposure.

Adverse reactions are presented per alphabetical system organ class and in decreasing order of frequency:

- **Cardiac disorders:** cyanosis, tachycardia;
- **Gastrointestinal disorders:** nausea, vomiting;
- **General disorders and administration site conditions:** chills;
- **Immune system disorders:** allergic reaction, anaphylactic reaction, angioedema;
- **Nervous system disorders:** headache, fainting, dizziness;
- **Respiratory, thoracic and mediastinal disorders:** throat irritation, wheezing, dyspnoea;
- **Skin and subcutaneous tissue disorders**: rash, itching, hives, erythema;
- **Vascular disorders:** hypotension, hypertension, flushing.

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).

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Intravenous Administration

Following intravenous administration for brain and renal imaging, technetium Tc 99m pentetate is distributed in the vascular compartment. It is cleared by the kidneys, which results in the ability to image the kidney. The images of the kidneys obtained in the first few minutes after administration of technetium Tc 99m pentetate represent the vascular pool within the kidney. Subsequent images of the kidneys represent radioactivity which is in the urine of both the collection system and the renal pelvis.

Technetium Tc 99m pentetate with intravenous administration tends to accumulate in intra-cranial lesions with excessive neovascularity or an altered blood-brain barrier. Technetium Tc 99m pentetate accumulation in the brain is prevented by an intact blood-brain barrier. It does not accumulate in the choroid plexus.

Aerosolized Inhalation Administration

Following inhalation of the aerosol, technetium Tc 99m pentetate deposits on the epithelium of ventilated alveoli. In patients with normal lungs, the deposition of technetium Tc 99m pentetate is homogeneous throughout the lungs. In patients with airway disease, the deposition patterns become inhomogeneous with irregular deposition of technetium Tc 99m pentetate in the airways and alveolar regions of the lung.

10.3 Pharmacokinetics

Absorption

Following inhalation, technetium Tc 99m pentetate was absorbed (T_{max} < 2 hours after inhalation) and distributed across the lung epithelium (bioavailability approximately 70%) and into the systemic circulation.

Distribution:

<u>Intravenous Administration</u>

Following intravenous administration, technetium Tc 99m pentetate is distributed throughout the extracellular fluid space and is cleared from the body by the kidney.

A variable percentage of the technetium Tc 99m pentetate binds to the serum proteins; this ranges from 3.7% following a single injection to approximately 10% if the material is

continuously infused. Although the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured renal clearance rate which is lower than that determined by inulin.

Technetium Tc 99m pentetate tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. It does not accumulate in the choroid plexus.

Inhalation Administration

When technetium Tc 99m pentetate is administered as a radio-aerosol for lung ventilation studies, a nebulizer produces a uniform population of finely dispersed droplets, ideally with a mass median aerodynamic diameter of about 0.5 mcm. When inhaled, the majority of the aerosol penetrates to the pulmonary alveoli with minimal deposition in the central airways. Technetium Tc 99m pentetate is rapidly absorbed by the lungs with half of the administered radioactivity being cleared from the lungs in approximately 60 minutes. It is subsequently cleared from the blood in a manner identical to that observed for the intravenously administered dose.

Metabolism: Technetium Tc 99m pentetate is not metabolized.

Elimination

Excretion

After either intravenous administration or inhalation, excretion is by glomerular filtration. The mean fraction of intravenously administered technetium Tc 99m pentetate excreted in urine over 24 hours was 102%. There is little or no binding of the chelate by the renal parenchyma.

11 STORAGE, STABILITY AND DISPOSAL

The unreconstituted reaction vials may be stored at or below room temperature (2 ºC to 30 ºC). After labelling with technetium Tc 99m, the radiopharmaceutical may also be stored at cool temperature (2 ºC to 8 ºC).

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

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

12 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.

Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclide, and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radionuclides.

13 PHARMACEUTICAL INFORMATION

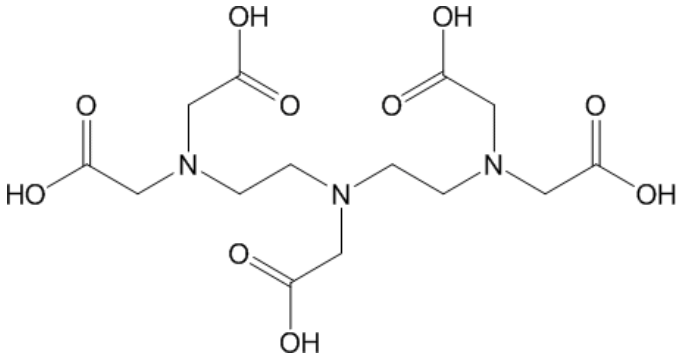
Drug Substance

Proper name: Pentetic Acid, USP (Diethylenetriaminepentaacetic Acid - [DTPA])

Chemical name: N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycine

Molecular formula and molecular mass: $C_{14}H_{23}N_3O_{10}$ and 393.349 $g \cdot mol^{-1}$

Structural formula of the chelate:



Physicochemical properties: White crystalline powder, free of any visible contamination.

Product Characteristics:

The kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Pentetate Injection for diagnostic use by intravenous injection or for inhalation after nebulization to a radio-aerosol.

Each 10 mL reaction vial contains 20 mg of pentetic acid, USP, 5 mg pf para-aminobenzoic acid, 3.73 mg of calcium chloride dihydrate, and 0.35 mg stannous chloride dihydrate in lyophilized white powder form under an atmosphere of nitrogen. Hydrochloric acid and/or sodium hydroxide has been used for pH adjustment. The pH of the reconstituted radiopharmaceutical is 6.5 to 7.5.

The addition of sterile, non-pyrogenic, and oxidant-free sodium pertechnetate Tc 99m solution produces a rapid labelling which is essentially quantitative and which remains stable *in vitro* throughout the 12-hour life of the preparation. No bacteriostatic preservative is present (preservative-free).

14 CLINICAL TRIALS

The clinical trial data on which the original indications were authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

A safety assessment was made using stannous pentetate complex in saline (but without added para-amino benzoic acid or technetium Tc 99m) in two rodent and one non rodent species. The acute toxicity was assessed by the intravenous administration over a dose range of 5 to 50 mg/kg. There were no signs of acute intoxication and after 14 days autopsy findings were negative. No pentetate-associated pathology has been observed in rats receiving a single exposure up to 9 times the recommended human dose administered by inhalation.

17 MANUFACTURER

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18 REGISTRATION HOLDER

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19 MARKETING AUTHORISATION NUMBER

134-63-29991-00

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