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

DIAGNOSTIC

For Intravenous Use

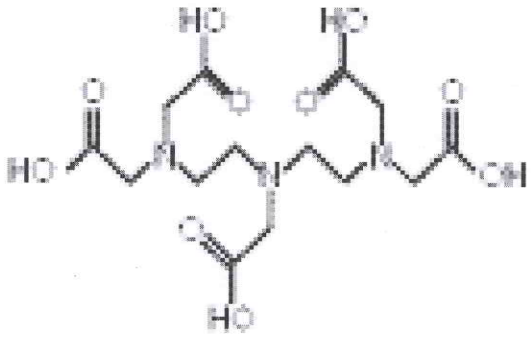
DESCRIPTION

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 20.0 mg of pentetic acid, 3.73 mg of calcium chloride dihydrate, 0.35 mg stannous chloride dihydrate, and 5.0 mg of p-aminobenzoic acid in lyophilized form under an atmosphere of nitrogen. Sodium hydroxide and/or hydrochloric acid 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.

The structure of the chelate is:



Its chemical name is N,N-bis[2-[bis(carboxymethyl)amino]ethyl] glycine.

® Registered Trademark of Jubilant DraxImage Inc.

ACTION

Intravenous Administration

Following its intravenous administration, technetium Tc-99m pentetate rapidly distributes itself throughout the extracellular fluid space from which it is promptly cleared from the body. The mechanism of excretion from the body is by glomerular filtration. There is little or no binding of the chelate by the renal parenchyma. 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 clearance rate which is lower than that determined with inulin.

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 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 radioaerosol 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 μm. 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.

INDICATIONS AND USAGE

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 a radio-aerosol, may be used to perform lung ventilation studies as an aid in the assessment of pulmonary embolic or obstructive airway disease.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

WARNINGS

None.

PRECAUTIONS

Intravenous Administration

The patient should be encouraged to drink fluid before and after the examination. To minimize the radiation dose to the bladder, the patient should be encouraged to void when the examination is completed and as often as possible thereafter for the next 4 to 6 hours.

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 radioaerosol 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 his mouth and expectorate into a disposable container.

General

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 preparation contains no bacteriostatic preservative. After labelling with technetium Tc-99m, the solution may be stored at or below room temperature (2 °C to 30 °C) in a suitable lead shield.

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.

The components of the kit are supplied sterile and non-pyrogenic. 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.

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.

Technetium Tc 99m Pentetate Injection as well as other radioactive drugs must be handled with care, and appropriate safety measures should be taken to minimize radiation exposure to the patients consistent with proper patient management, and to minimize radiation exposure to clinical personnel.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc 99m Pentetate Injection affects fertility in males or females. Mutagenesis studies have not been conducted.

Pregnancy and Teratogenicity

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Pentetate Injection. It is also 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 been no studies in pregnant women. Technetium Tc 99m Pentetate Injection should be given to a pregnant woman only if clearly needed.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers

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

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

ADVERSE REACTIONS

Pyrogenic and allergic reactions to technetium Tc-99m pentetate preparations have been reported in the literature.

PHARMACOLOGY

Intravenous Administration

Studies in rabbits and mice were made following the intravenous administration of technetium Tc-99m pentetate without PABA. Rapid blood clearance and urine excretion were noted in both species.

The blood disappearance was more rapid in mice with less than 4 % of the injected dose remaining after 15 minutes. The amount decreased to approximately 1 % and 0.5 % at 30 minutes and one hour post injection, respectively. Urine excretion reached 85 % and 95 % of the dose at the end of 1 and 3 hours, respectively. No kidney retention was noted.

These rates were similar, but somewhat slower in rabbits. The blood value fell to less than 7 % by 1 hour and to 2 % by 3 hours. Urine excretion was 63 % and 86 % of the injected dose after 1 and 3 hours, respectively.

TOXICOLOGY

A safety assessment was made using stannous pentetate complex in saline (but without added p-aminobenzoic 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.

PHYSICAL CHARACTERISTICS

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

Table 1

Principal Radiation Emission Data

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

External Radiation

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

Table 2

Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

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

Table 3

Physical Decay Chart of Technetium Tc-99m Half-Life: 6.02 hours

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

*Calibration Time

RADIATION DOSIMETRY

Intravenous Administration

The estimated absorbed radiation doses[2] to various organs of an average patient (70 kg) from an intravenous injection of maximum doses of 185 MBq (5 mCi) and 740 MBq (20 mCi) of Technetium Tc 99m Pentetate Injection are shown in Table 4.

Table 4

Estimated Absorbed Radiation Doses Delivered by Intravenous Administered Tc-99m Pentetate

	Kidney Imaging or GFR estimation		Brain Imaging or Assessment of Renal Perfusion	
Organ	mGy/ 185 MBq	rads/ 5 mCi	mGy/ 740 MBq	rads/ 20 mCi
Kidneys	4.5	0.45	18.0	1.8
Bladder Wall				
2.0 hr void	5.75	0.58	23.0	2.3
4.8 hr void	13.5	1.35	54.0	5.4
Testes				
2.0 hr void	0.38	0.04	1.5	0.15
4.8 hr void	0.53	0.05	2.1	0.21
Ovaries				
2.0 hr void	0.55	0.06	2.2	0.22
4.8 hr void	0.78	0.08	3.1	0.31
Whole Body	0.3	0.03	1.2	0.12

Inhalation Administration

The estimated absorbed radiation dose to the lungs of an adult (70 kg) from an inhaled dose of 5.2 MBq (140 μCi) of nebulized technetium Tc-99m pentetate is 0.023 rads. Absorbed radiation doses delivered to several organs of an adult patient (70 kg) following deposition of 7.4 MBq (200 μCi) of the radio-aerosol in the lungs are shown in Table 5.

Table 5

Estimated Absorbed Radiation Doses From Tc-99m Pentetate Administered by Inhalation

Organs	mGy/7.4 MBq	rads/200 μCi
Kidneys	0.08	0.008
Bladder	0.02	0.002
Testes	1.26	0.126
Ovaries	0.04	0.004
Whole Body	0.06	0.006

Absorbed doses to most organs are usually significantly less than doses delivered after intravenous administration of the radiopharmaceutical. However, some aerosol systems may expose the patient to 10 % of the dose placed in the nebulizer.

DOSAGE AND ADMINISTRATION

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. Withdrawal for administration must be made aseptically.

To minimize the radiation dose to the bladder, the patient should be encouraged to increase fluid intake, and to void when the examination is completed and as often as possible thereafter for the next 4 to 6 hours.

Store the finished preparation at or below room temperature (2 °C to 30 °C) in a suitable lead shield.

Using proper shielding, parenteral drug products should be inspected for particulate matter and discoloration prior to administration. Do not use if the solution contains particulate matter or is not a clear solution.

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:

Kidney imaging and glomerular
filtration rate estimation.....111 to 185 MBq (3 to 5 mCi)

Brain imaging or assessment
of renal perfusion.....370 to 740 MBq (10 to 20 mCi)

Dosage for Inhalation Administration

For aerosol administration, place the required volume and quantity of radioactivity (0.37 to 1.67 GBq [10 to 45 mCi]) of technetium Tc-99m pentetate in the nebulizer and follow the manufacturer's directions for nebulization and administration of the radio-aerosol.

DIRECTIONS FOR PREPARATION

The preparation of Technetium Tc 99m Pentetate Injection may be accomplished by the following procedure. Use aseptic procedures throughout and take precautions to minimize radiation exposure by the use of suitable shielding. Waterproof gloves should be worn during the preparation procedure.

Before reconstituting a vial it should be inspected for cracks and/or a melted plug or any other indication that the integrity of the vacuum seal has been lost.

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

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

Intravenous Administration

To prepare Technetium Tc 99m Pentetate Injection:

1. Write in the space provided on the label the date and time of preparation. Apply the label to the shielded vial.

2. Remove the protective disc from the reaction vial and swab the closure with an alcohol swab.

3. 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 gigabecquerels (500 mCi). Sodium pertechnetate Tc-99m solutions containing an oxidizing agent are not suitable for use.

4. Using a shielded syringe, aseptically add the sodium pertechnetate Tc-99m solution to the reaction vial, while avoiding the build-up of excessive pressure in the vial. Pressure 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.

5. 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.

6. Assay the product in a suitable calibrator, record the radioassay information on the label with radiation warning symbol.

7. The radiochemical purity of the finished preparation should be determined prior to patient administration. The radiochemial purity should not be less than 90 %.

8. 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.

9. The finished preparation should be stored at or below room temperature (2 °C to 30 °C) and 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.

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 % Soium 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 of the acetone sample 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 (Rf 0), while the bound and free technetium $^{99m}TcO_4^-$ move to the front of Rf 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 Rf 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:

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

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.

HOW SUPPLIED

DRAXIMAGE® DTPA

Kit for the preparation of Technetium Tc 99m Pentetate Injection

Product No. 500170

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

Pentetic acid	20.0 mg
p-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.

STORAGE

The unreconstituted reaction vials should be stored at or below room temperature (2 °C to 30 °C). After labelling with technetium Tc-99m, the radiopharmaceutical should also be stored at or below room temperature (2 °C to 30 °C).

EXPIRY

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

REFERENCES

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

2. Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

Registration number: 134 63 29991 00

Name of manufacturer: JUBILANT DRAXIMAGE INC., CANADA

License Holder: SOREQ NUCLEAR RESEARCH CENTRE

Revised: October 2010

Jubilant DraxImage Inc.
Kirkland Quebec H9H 4J4 Canada