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

DIAGNOSTIC

For Intravenous Use

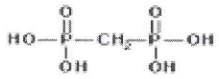
DESCRIPTION

The kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Medronate Injection for diagnostic use by intravenous injection.

Each 10 mL reaction vial contains 10.0 mg of medronic acid (as the sodium salt), 1.1 mg of stannous chloride dihydrate, and 2.0 mg of p-aminobenzoic acid in lyophilized form under an atmosphere of nitrogen. Sodium hydroxide and/or hydrochloric acid have been used for pH adjustment. 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-hours life of the preparation. The pH of the reconstituted radiopharmaceutical is 6.5 to 7.5. No bacteriostatic preservative is present.

The precise structure of the reaction vial complex or of its technetium labelled form is not known at this time.

The structural formula of medronic acid is:



ACTION

When injected intravenously, technetium Tc-99m medronate is rapidly cleared from the blood; about 50 % of the dose is accumulated and retained by the skeleton, while the remaining 50 % is excreted in the urine within twenty-four hours. About 10 % of the injected dose remains in the blood at one hour post-injection, 5 % at 2 hours, and less than 1 % remains at twenty-four hours. The resultant blood clearance curve is tri-exponential with the two fastest components accounting for all but a few percent of the injected dose.

Following intravenous administrations of technetium Tc-99m medronate, skeletal uptake occurs as a function of blood flow to bone and bone efficiency in extracting the complex. Bone mineral crystals are generally considered to be hydroxyapatite, and the complex appears to have an affinity for the hydroxyapatite crystals in the bone.

The rapid blood clearance provides bone to soft-tissue ratios which favour early imaging. The skeletal uptake is bilaterally symmetrical and is greater in the axial skeleton than in the long bones. Areas of abnormal osteogenesis show altered uptake making it possible to visualize a variety of osseous lesions.

INDICATIONS AND USAGE

Technetium Tc 99m Medronate Injection is a skeletal imaging agent used to demonstrate areas of altered osteogenesis as seen, for example, in metastatic bone disease, Paget's disease, arthritic disease and osteomyelitis.

CONTRAINDICATIONS

Hypersensitivity to this compound.

WARNINGS

The diphosphonate class of compounds is known to complex cations such as calcium and can create hypocalcemia as observed in animal models (see TOXICOLOGY). Therefore, caution should be exercised when administering this agent to patients who have, or who may be predisposed to hypocalcemia (i.e., alkalosis).

Preliminary reports indicate impairment of brain images using Sodium Pertechnetate Tc 99m Injection which have been preceded by bone imaging using an agent containing stannous ions. The impairment may result in false-positive or false-negative brain images. It is recommended, where feasible, that brain imaging using Sodium Pertechnetate Tc 99m Injection precede bone imaging procedures. Alternatively, a brain imaging agent such as technetium Tc-99m pentetate may be employed.

PRECAUTIONS

The finding of an abnormal concentration of radioactivity implies the existence of underlying pathology, but further study is required to distinguish benign from malignant lesions.

Optimal imaging results are obtained 1 to 4 hours after administration. The quality of the image may be affected by obesity, old age, and impaired renal function.

To minimize the radiation dose to the urinary bladder, the patient should be encouraged to increase his fluid intake and to void as often as possible after the injection of technetium Tc-99m medronate, and for 4 to 6 hours after the imaging procedure.

General

Contents of the reaction vial are intended only for use in the preparation of Technetium Tc 99m Medronate Injection and are **NOT** to be administered directly to the patient.

The preparation contains no bacteriostatic preservative. The solution should not be used if it is cloudy.

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 a 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 Medronate 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.

The contents of the kit before preparations are not radioactive. However, after the sodium pertechnetate Tc-99m is added, adequate shielding of the final preparation must be maintained.

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 Medronate 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 Medronate Injection. It is also not known whether Technetium Tc 99m Medronate 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 Medronate 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

Hypersensitivity reactions such as fever, rash, swelling, chills, nausea, and dizziness have occurred infrequently following the administration of Technetium Tc 99m Medronate Injection.

ANIMAL PHARMACOLOGY

Studies conducted in mice and rabbits demonstrated a rapid distribution of technetium Tc-99m medronate between bone and urine. At the end of one hour, less than 1 % of the dose remained in the blood of mice with 80 to 90 % of the radioactivity being divided equally between the bone and urine. In rabbits, the blood clearance was slower, but the percent of the dose remaining in bone and urine was similar to that in mice.

TOXICOLOGY

A safety assessment using stannous medronate complex reconstituted with saline but without technetium Tc-99m or p-aminobenzoic acid has been made in two rodent and one non-rodent species.

In mice, an intravenous injection of 100 mg/kg (2 mg/0.2 mL/20 g) induced severe clonic convulsions. No mortalities and no gross pathological changes were discovered over a 14 day observation period. A lower dose of 40 mg/kg showed no signs of intoxication and the gross necropsy was negative. Similar results were obtained in rats and beagle dogs at 20 mg/kg.

The human dose using this formulation is variable depending on the number of examinations made from the contents of one vial. In the event that this becomes a single dose of 10 mg per 70 kg or 0.15 mg/kg, these results indicated a safety factor of at least 100.

The toxicity of medronic acid has been reported to be the same as that for the ethylene-hydroxy-diphosphonate (EHDP) (intravenous LD_{50} 45 to 55 mg/kg) in mice and rabbits. Other reports showed a maximum (LD_{100}) lethal dose of EHDP in mice to be 200 mg/kg with no deaths occurring at 100 mg/kg. The LD_{50} in rabbits and rats was 40 to 70 mg/kg on rapid injection of EHDP, whereas slow injection raised this to 70 to 100 mg/kg. It was demonstrated in a variety of experimental animals that acute toxic symptoms of tachycardia, hyperpnea, and tetany began at 20 to 30 mg/kg. These changes were considered consistent with the induction of hypocalcemia.

The role played by tin chelation, dilution, and speed of injection as factors in explaining the variable results of toxicity studies has been discussed in the literature.

A 14 day subacute toxicity study of stannous medronate complex was performed in mice and cats. In cats, pyelonephritis was observed in the test groups as well as in some of the control animals. Associated renal tubular calcification was noted only in the dosed cats. Minimal focal calcification was observed in the liver and heart of one mouse in the high dose group. No other significant toxicological findings were noted. The cumulative low doses in cats and in mice were 65 and 87 times greater, respectively, than the maximum probable human dose on a mg/kg basis, while the cumulative high doses were 490 and 866 times greater, respectively.

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 % / 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

The estimate absorbed radiation doses[2] to various organs of an average patient (70 kg) from an intravenous injection of a maximum dose of 740 megabecquerels (20 mCi) of Technetium Tc 99m Medronate Injection are shown in Table 4. The effective half-life is assumed to be the physical half-life for all calculated values.

Table 4

Estimated Absorbed Radiation Doses

Organ / Tissue	mGy / 740 MBq	Rads / 20 mCi
Total Body	1.3	0.13
Total Bone	7.0	0.70
Red Marrow	5.6	0.56
Kidneys	8.0	0.80
Liver	0.6	0.06
Bladder Wall		
2.0 hr void	26.0	2.60
4.8 hr void	62.0	6.20
Ovaries		
2.0 hr void	2.4	0.24
4.8 hr void	3.4	0.34
Testes		
2.0 hr void	1.6	0.16
4.8 hr void	2.2	0.22

DOSAGE AND ADMINISTRATION

The recommended adult dose of Technetium Tc 99m Medronate Injection is 370 to 740 MBq (7.4 MBq/kg) [10 to 20 mCi (200 μCi/kg)] by slow intravenous injection over a period of 30 seconds. Optimum scanning time is 1 to 4 hours post-injection.

To minimize the contribution of the bladder content to the image, the patient should void immediately before imaging is started.

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

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.

DIRECTIONS FOR PREPARATION

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

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

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

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

To prepare Technetium Tc 99m Medronate Injection:

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

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 GBq (500 mCi). Sufficient sodium pertechnetate is to be used for the reconstitution of a reaction vial to ensure that the dose of medronate administered does not exceed 10 mg. 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 build up 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. The procedure is repeated as necessary until the entire amount of pertechnetate is added to the vial and normal pressure is established within the vial.

5. Place the lead cap on the vial shield and 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) after mixing. 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 radiochemical 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 discarded after12 hours. It should also be retained during its life in a lead vial shield with the lead cap in place.

Radiochemical Purity

Chromatographic Methods

The following procedure describes a series of simple steps for running chromatograms. 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 (Fisher Scientific No. 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 (Rf 0), while the bound and free technetium $^{99m}TcO_4^-$ move to the front 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 end. 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 pertechnetate 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:

$$\text{Percent chelated } {}^{99m}\text{Tc} = 100 - \%\ {}^{99m}\text{TcO}_4^-$$

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® MDP

Kit for the preparation of Technetium Tc 99m Medronate Injection
Product No. 500210

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

Medronic acid (as Na salt)	10.0 mg
Para-aminobenzoic acid	2.0 mg
Stannous chloride dihydrate	1.1 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 discarded12 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. Method of Calculation: Snyder, W.S.; Ford, M.R.; Warner, G.G.; Watson, S.B.: "S" Absorbed dose per unit cumulated activity for selected radionuclides and organs, MIRD Pamphlet No. 11, 1975.

Registration number: 134 64 29992 00

Name of manufacturer: JUBILANT DRAXIMAGE INC., CANADA

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