OSTEOLITE®
Kit for the Preparation of
Technetium Tc 99m Medronate Injection

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of
Medronate Disodium - 10mg
Stannous Chloride, minimum ($SnCI_2 \bullet 2H_20$)- 0.6mg
Total Tin, maximum ($SnCI_2 \bullet 2H_20$) - 1.15mg
Prior to lyophilization, the pH is adjusted to between 7.0-7.5 with HCI and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

Administration is by intravenous injection for diagnostic use, after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection.

The precise structure of stannous technetium medronate complex is known at this time (JACS Vol.102, 2476, 1980).

Physical Characteristics

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] Photons that are useful for imaging studies are listed in Table 1.

Table 1. Principal Radiation Emission Data

Radiation	Mean %/Disintegration	Mean 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 Tc99m is 5.4 microcoulombs/kg-MBq-hr (0.78 R/mCi-hr) at 1cm. The first half value layer is 0.017cm of Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of lead (Pb) is shown In Table 2. To facilitate control of the radiation exposure from MBq (mCi) amounts of this radionuclide, the use of 0.25cm thickness of lead (Pb) will attenuate the radiation emitted by a factor of 1,000.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness	Coefficient of Attenuation
lead (Pb) cm	0.5
0.017	10^{-1}
0.08	10^{-2}
0.16	10^{-3}
0.25	10^{-4}
0.33	10^{-5}

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; Technetium Tc99m Hall-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

CLINICAL PHARMACOLOGY: During the initial twenty-four hours following intravenous injection of Technetium Tc99m Medronate, about 50% of the dose is retained in the skeleton, and about 50% is renally excreted; less than 2% of the injected dose remains in the vascular system. Blood levels fall to 3-5% of the injected dose by three hours post-injection.

Upon intravenous injection, osseous uptake of Technetium Tc99m Medronate appears to be related to bone metabolic activity and to skeletal blood flow. Technetium Tc99m Medronate exhibits a specific affinity for areas of altered osteogenesis.

INDICATIONS AND USAGE: Technetium Tc99m Medronate may be used as a bone Imaging agent to delineate areas of altered osteogenesis.

CONTRAINDICATIONS: None known.

WARNINGS: This class of compounds is known to complex cations such as calcium. Particular caution should be used with patients who have, or who may be predisposed to, hypocalcemia (i.e. alkalosis).

Preliminary reports indicate impairment of brain scans using Sodium Pertechnetate Tc99m Injection which have been preceded by a bone scan using an agent containing stannous ions. The impairment may result in false-positive or false-negative brain scans It is recommended, where feasible, that brain scans precede bone imaging procedures.

Alternatively, a brain imaging agent such as Technetium Tc99m Pentetate may be used.

The biodistribution of technetium Tc 99m medronate may be altered in the presence of high levels of certain cations (iron, calcium, and aluminum). This may result in reduced uptake of radionuclide in the skeleton and increased extraosseal uptake, which may potentially degrade imaging quality. High levels of these cations may be caused by concomitant medications or medical conditions (e.g., iron overload, hypercalcemia, etc.). Most cases were observed after iron infusion. (See **PRECAUTIONS, Drug Interactions.**)

PRECAUTIONS: To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake and to void as often as possible after the Injection of Technetium Tc99m Medronate. and for 4 to 6 hours alter the imaging procedure.

The preparation contains no bacteriostatic preservatives. Technetium Tc99m Medronate should be used within six hours of preparation.

General

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Medronate and are NOT to be administered directly to the patient.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to the patients consistent with proper patient management.

Contents of the kit before preparation are not radioactive. However, after the Sodium Pertechnetate Tc99m Injection is added, adequate shielding of the final preparation must be maintained.

The components of the kit are sterile and non-pyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation.

Technetium Tc99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used.

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.

Drug Interactions

The biodistribution of technetium Tc 99m medronate may be altered in the presence of high levels of certain cations (iron, calcium, and aluminum). This may result in reduced uptake of radionuclide in the skeleton and increased extraosseal uptake, which may potentially degrade imaging quality. In patients with high levels of these cations caused by concomitant medications, particularly patients receiving iron infusions, consider performing an imaging study with technetium Tc 99m medronate injection once the cation levels have normalized (e.g., after 3 to 5 half-lives of the cation). (See **WARNINGS**.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc99m Medronate affects fertility in males or females.

Pregnancy

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Medronate. It is also not known whether Technetium Tc99m Medronate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Medronate should be given to a pregnant woman only if clearly needed.

Ideally, examinations using radiopharmaceuticals, especially those electives 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 Tc99m is excreted in human milk during lactation; therefore, formula feedings should be substituted for breast feedings.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function. care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS: Several cases of allergic dermatological reactions have been reported in association with the use of Osteolite. In addition, one case of cardiac arrest in a patient also undergoing pulmonary function testing one and one-half hours after the performance of an Osteolite scan has been reported.

Several reactions have also been reported in association with other radiopharmaceuticals of the diphosphonate class, particularly Technetium Tc99m Medronate. These are usually hypersensitivity reactions characterized by itching, various skin rashes, hypotension, chills, nausea, fever and vomiting.

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration to be employed in the average patient (70kg) is:

- 370 to 740 MBq (10-20mCi)

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

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

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

Store at controlled room temperature (20- 25°C) before and after reconstitution.

Instructions for Preparation of Technetium Tc 99m Medronate Injection

Preparation of Technetium Tc99m Medronate from Kit for the Preparation of Technetium Tc99m Medronate is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the vial, write the estimated activity, date and time of preparation in the space provided on the vial label. Then tear off a radiation symbol and attach it to the neck of the vial.
b. Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the vial and swab the top of the vial closure with alcohol to sanitize the surface.
c. Place the reaction vial in a suitable radiation shield with a fitted radiation cap.
d. With a sterile, shielded syringe, aseptically obtain 2-8ml [maximum 7.4 GBq (200mCi)] of a suitable, oxidant-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection.
e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial.
f. Place the radiation shield cap on the vial shield and swirl the contents of the vial for one minute and let stand for 1-2 minutes.
g. Maintain adequate shielding during the life of the product by using the radiation vial shield with the radiation shield cap in place and by using a syringe shield for withdrawing and injecting the preparation.
h. Using proper shielding, the vial containing the reconstituted solution should be visually inspected to ensure that it is free of particulate matter prior to injection. Do not use if the solution is cloudy.
i. Assay the product in a suitable dose calibrator, then complete and affix the "radioactive contents" label to the vial shield
j. Aseptically withdraw material for use within six (6) hours. Store reconstituted vial at controlled room temperature (20- 25°C). The vial contains no preservative

Radiation Dosimetry

The estimated absorbed radiation doses[2] to organs and tissues of an average patient (70kg) from an intravenous injection of 740 MBq (20mCi) of Technetium Tc99m Medronate are shown in Table 4.

Table 4. Radiation Absorbed Doses

Organ	Radiation mGy/740MBq	Absorbed Dose (rads/20mCi)
Total Body	1.3	(0.13)
Bone Total	7.0	(0.70)
Red Marrow	5,6	(0.56)
Kidneys	8.0	(0.80)
Liver	0.6	(0.06)

Bladder wall		
2 hr void	26.0	(2.60)
4.8 hr void	62.0	(6.20)
Ovaries		
2 hr void	2.4	(0.24)
4.8 hr void	3.4	(0.34)
Testes		
2 hr void	1.6	(0.16)
4.8 hr void	2.2	(0.22)

[2]Method of Calculation: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

HOW SUPPLIED: OSTEOLITE® Kit for use in the preparation of Technetium Tc99m Medronate for Injection is supplied in kits of five (5) or thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is adjusted to between 7.0-7.5 with hydrochloric acid and/or sodium hydroxide solution. The contents of the vial are lyophilized and stored under nitrogen. Store at controlled room temperature (20 - 25°C) before and after reconstitution. Technetium Tc99m Medronate contains no preservatives. Included in each live (5) vial kit is one (1) package insert and twelve (12) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and seventy-two (72) radiation labels.

This reagent kit for the preparation of a radiopharmaceutical is approved for use by persons licensed pursuant to Section 120.533, Code of Massachusetts Regulation 105, or under equivalent license of the U.S. Nuclear Regulatory Commission or an Agreement State.

Marketed by
CIS·US, Inc.
10 DeAngelo Drive
Bedford, MA, USA 01730

The drug product is not being marketed.

Revised: 05/2025

Kit for the Preparation of Technetium Tc 99m Medronate for Injection

DIAGNOSTIC FOR INTRAVENOUS USE

Rx Only

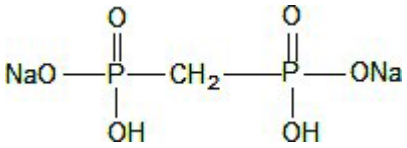
DESCRIPTION:

Kit for the Preparation of Technetium Tc 99m Medronate is a multidose reaction vial which contains the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Medronate Injection for diagnostic use by Intravenous injection.

Each 10mL multidose vial contains:

Medronic Acid: 20 mg Ascorbic acid: 1mg
Stannous fluoride, SnF_2: 0.13mg (minimum)
Total tin (maximum, as stannous fluoride, SnF_2): 0.38mg

The pH is adjusted to 6.5 (6.3 to 6.7) with sodium hydroxide and/or hydrochloric acid prior to lyophilization. No bacteriostatic preservative is present in the vial. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture. The structural formula is:



When a solution of sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc 99m Injection is added to the vial, the diagnostic agent, Technetium Tc 99m Medronate is formed for administration by intravenous injection. The pH of the reconstituted product is 5.4 to 6.8. The precise structure of Technetium Tc 99m Medronate Injection is not known at this time.

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 Date

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

[1]Kocher, DC: Radioactive Decay Data Tables, DOE/TIC-11026, 108, 1981

EXTERNAL RADIATION:

The specific gamma ray constant for Tc 99m is 0.78 R/millicurie-hr at 1 cm. The first half-value layer is 0.017 cm of lead (Pb). A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of the various thicknesses of Pb is shown in Table 2. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

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: Tc 99m, 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

CLINICAL PHARMACOLOGY:

During the initial 24 hours following intravenous injection of Technetium Tc 99m Medronate, about 50% of each dose is retained in the skeleton, and about 50% is excreted in the urine. Upon intravenous injection, Technetium Tc 99m Medronate exhibits a specific affinity for areas of altered osteogenesis. In humans, blood levels fall to 4 to 10% of the injected dose by two hours post-injection and to 3 to 5% by three hours.

Uptake of Technetium Tc 99m Medronate Injection in bone appears to be related to osteogenic activity and to skeletal blood perfusion. The deposition in the skeleton is bilaterally symmetrical, with increased accumulation in the axial structure as compared to the appendicular skeleton. There is increased activity in the distal aspect on long bones as compared to the diaphyses.

INDICATIONS AND USAGE:

Technetium Tc 99m Medronate Injection may be used as a bone imaging agent to delineate areas of altered osteogenesis.

CONTRAINDICATIONS:

None Known.

WARNINGS:

This class of compounds is known to complex cations such as calcium. Particular caution should be used with patients who have, or may be predisposed to hypocalcemia (i.e., alkalosis).

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

The biodistribution of technetium Tc 99m medronate may be altered in the presence of high levels of certain cations (iron, calcium, and aluminum). This may result in reduced uptake of radionuclide in the skeleton and increased extraosseal uptake, which may potentially degrade imaging quality. High levels of these cations may be caused by concomitant medications or medical conditions (e.g., iron overload, hypercalcemia, etc.). Most cases were observed after iron infusion. (See **PRECAUTIONS, Drug Interactions**.)

PRECAUTIONS:

General

Contents of the 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.

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

To minimize radiation dose to the bladder, the patients should be encouraged to drink fluids and to void immediately before the examination and as often thereafter as possible for the next 4 to 6 hours.

Technetium Tc 99m Medronate Injection should be formulated within six (6) hours prior to clinical use. Optimal imaging results are obtained 1 to 4 hours after administration.

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.

The image quality may be adversely affected by obesity, old age, or impaired renal function.

The components of the kit are sterile and non-pyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation. Technetium Tc 99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used.

The preparation contains no bacteriostatic preservative. Technetium Tc 99m Medronate Injection should be stored at 20-25^{0}C (68-77^{0}F) and discarded 6 hours after reconstitution. The solution should not be used if the contents are cloudy.

Vials are sealed under nitrogen: air or oxygen is harmful to the contents of the vials and the vials should not be vented.

The components of the Kit for the Preparation of Technetium Tc 99m Medronate for Injection are supplied sterile and non-pyrogenic. Aseptic procedures normally employed in making additions and withdrawals for sterile, non-pyrogenic containers should be used during the addition of the pertechnetate solution and the withdrawal of doses for patient administration. Shielding should be utilized when preparing Technetium Tc 99m Medronate Injection.

No special handling is required for the non-radioactive drug product.

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.

Drug Interactions

The biodistribution of technetium Tc 99m medronate may be altered in the presence of high levels of certain cations (iron, calcium, and aluminum). This may result in reduced uptake of radionuclide in the skeleton and increased extraosseal uptake, which may potentially degrade imaging quality. In patients with high levels of these cations caused by concomitant medications, particularly patients receiving iron infusions, consider performing an imaging study with technetium Tc 99m medronate injection once the cation levels have normalized (e.g., after 3 to 5 half-lives of the cation). **(See WARNINGS.)**

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

Animal reproduction and teratogenicity studies have not been conducted on 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. 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, on 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 Medronate Injection is excreted in human milk during lactation; therefore, formula feeding should be substituted for breast feeding.

Pediatric Use

Safety and effectiveness in pediatric subjects have not been established.

ADVERSE REACTIONS:

Several adverse reactions due to Technetium Tc 99m Medronate Injection have been reported. These were usually hypersensitivity reactions characterized by itching, various skin rashes, hypotension, chills, nausea and vomiting. There have also been rare cases of dizziness and asthenia associated with the use of Technetium Tc 99m Medronate.

DOSAGES AND ADMINISTRATION:

Shielding should be utilized when preparing Technetium Tc 99m Medronate Injection.

After preparation with oxidant-free Sodium Pertechnetate Tc 99m Injection, the suggested dose range of Technetium Tc 99m Medronate Injection in the average ADULT patient (70kg.) is:

370-740 megabecquerels: (10-20 millicuries) given intravenously.
Imaging is optimal at 1 to 4 hours post injection.

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

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

Radiation Dosimetry

The effective half-life was assumed to be the physical half-life for all calculated values. The estimated radiation absorbed doses to an average ADULT patient (70kg) from an intravenous injection of a maximum of 740 megabecquerels (20 millicuries) of Technetium Tc 99m Medronate Injection are shown in Table 4.

TABLE 4

Estimated Absorbed Radiation Dose[2]

Technetium Tc 99m Medronate

Organ		(MGy/740 MBq)	(Rads / 20 mCl)
Total Body		1.3	0.13
Bone Total		7.0	0.70
Red Marrow		5.6	0.56
Kidneys		8.0	0.80
Liver		0.6	0.06
Bladder Wall	2 hour void	26	2.60
	4.8 hour void	62	6.20
Ovaries	2 hour void	2.4	0.24
	4.8 hour void	3.4	0.34
Testes	2 hour void	1.6	0.16
	4.8 hour void	2.2	0.22

[2]Method of calculation: "S" Absorbed Dose Per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No 11 (1975)

HOW SUPPLIED:

Kit for the Preparation of Technetium Tc 99m Medronate Injection is supplied in kits of five (5) or thirty (30) sterile, non-pyrogenic vials. Each 10 mL multidose vial contains 20 mg medronic acid, 1mg ascorbic acid, 0.13 mg minimum stannous fluoride (SnF2) and 0.38 mg maximum total tin, as stannous fluoride, SnF2 in lyophilized form. The pH is adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization. The vial does not contain a preservative. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture. The pH of the reconstituted product is 5.4 to 6.8.

Kit Contents

Included in each five (5) vial kit is one (1) package insert and ten (10) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and sixty (60) radiation labels.

Storage

Store the product as supplied at 20-25^{0}C (68-77^{0}F) [See USP]. After reconstitution store at 20-25^{0}C (68-77^{0}F) [See USP] **(see DOSAGE AND ADMINISTRATION).**

DIRECTIONS FOR PREPARATION OF TECHNETIUM Tc 99m MEDRONATE INJECTION:

Procedural Precautions

The lyophilized powder in the reaction vial is sterile and non-pyrogenic and does not contain a preservative. Shielded syringes and aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during addition of pertechnetate solution to the reaction vial and the withdrawal of doses for patient administration.

If sodium pertechnetate Tc 99m must be diluted prior to injection into the reaction vial, only Sodium Chloride Injection USP 0.9% (without preservatives) should be used.

Technetium Tc 99m Medronate Injection is prepared from Kit for the Preparation of Technetium Tc 99m Medronate Injection by the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure.

   Remove the plastic disk from the vial and swab the top of the vial closure with alcohol to sanitize the surface.

2. Complete the radiation label and affix to the vial. Place the reaction vial in a suitable radiation shield.
3. With a sterile, shielded syringe aseptically obtain 0.5-5 mL, of a suitable, oxidant- free, sterile, non-pyrogenic Sodium Pertechnetate Tc 99m Injection containing no more than 18.5 gigabecquerels (500 millicuries). Aseptically add the Sodium Pertechnetate Tc 99m Injection to the vial. Be sure to maintain a nitrogen atmosphere in the vial by not introducing air during reconstitution.
4. Swirl the contents of the vial for one minute, and let stand for at least 10 minutes.
5. Record time and date of preparation.
6. The radiochemical purity of the prepared radiopharmaceutical should be checked prior to patient administration.
7. Examine vial contents for particulates and discoloration prior to injection. Do not use if solution is cloudy.
8. Withdrawals for administration must be made aseptically using a sterile shielded syringe and needle. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be vented. If repeated withdrawals are made from a vial, the replacement of contents with air should be minimized.
9. Use within six (6) hours of preparation. For optimum results, this time should be minimized. The vial contains no bacteriostatic preservative. After reconstitution store at 20-25ºC (68-77ºF) [See USP].
10. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

NDC# 045567-0040-1 (5 vial pack)

NDC# 045567-0040-2 (30 vial pack)

This reagent kit for the preparation of a radiopharmaceutical is approved for use by per- sons licensed pursuant to Section 120.547, Code of Massachusetts Regulation 105, or under equivalent license of the U.S. Nuclear Regulatory Commission or an Agreement State.

Manufactured By:

Sun Pharmaceutical Industries, Inc.

Billerica, MA 01821

1-800-221-7554

(For International, call 781-275-7120)

PL-000007 Printed in U.S.A

Rev 2 May 2025

Kit for the Preparation of
Technetium Tc 99m Pyrophosphate Injection

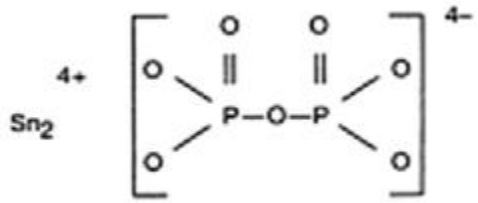
For Diagnostic Use
Rx Only

DESCRIPTION

Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection is a multidose reaction vial which contains the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Pyrophosphate Injection for diagnostic use by intravenous injection.

Each 10 mL vial contains 12.0 mg of sodium pyrophosphate, 2.8 mg minimum stannous tin as stannous chloride dihydrate and 4.9 mg maximum total tin as stannous chloride dihydrate; pH is adjusted to 5.3-5.7 with hydrochloric acid prior to lyophilization. No bacteriostatic preservative is present. Sealed under nitrogen.

The chemical names are: (1) Diphosphoric acid, Ditin (2^+) salt; (2) Ditin (2^+) pyro- phosphate (4^-). The structural formula is:



When a solution of sterile, non-pyrogenic, oxidant-free isotonic Sodium Pertechnetate Tc 99m Injection U.S.P. is added to the vial, Technetium Tc 99m Pyrophosphate Injection is formed for intravenous administration.

When a solution of sterile, non-pyrogenic, isotonic saline is added to the vial, it forms a blood pool imaging agent when Sodium Pertechnetate Tc 99m Injection is injected intravenously 30 minutes after the intravenous administration of the non-radioactive reconstituted Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection. The precise structure of Technetium Tc 99m Pyrophosphate Injection is not known at this time.

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 Percent Per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

[1]Kocher DC: Radioactive decay data tables. ***DOE/TIC-11026:*** 108, 1981

External Radiation

The specific gamma ray constant for Tc 99m is 0.78 R/hr-millicurie at 1 cm. The first half-value layer is 0.017 cm of lead (Pb). 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 a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

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: Tc 99m, 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

CLINICAL PHARMACOLOGY

When injected intravenously, Technetium Tc 99m Pyrophosphate Injection has a specific affinity for areas of osteogenesis. It is also concentrated in the injured myocardium, primarily in areas of irreversibly damaged myocardial cells.

One to two hours after intravenous injection of Technetium Tc 99m Pyrophosphate Injection, an estimated 40 to 50 percent of the injected dose has been taken up by the skeleton, and approximately 0.01 to 0.02 percent per gram of acutely infarcted myocardium. Within a period of one hour, 10 to 11 percent remains in the vascular system, declining to approximately 2 to 3 percent twenty-four hours post injection. The average urinary excretion was observed to be about 40 percent of the administered dose after 24 hours.

The non-radioactive reconstituted Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection also has an affinity for red blood cells. When administered 30 minutes prior to the intravenous administration of Sodium Pertechnetate Tc 99m Injection,

approximately 76 percent of the injected activity remains in the blood pool providing excellent images of the cardiac chambers.

INDICATIONS AND USAGE

Technetium Tc 99m Pyrophosphate Injection is a bone imaging agent used to demonstrate areas of altered osteogenesis, and a cardiac imaging agent used as an adjunct in the diagnosis of acute myocardial infarction.

Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection is a blood pool imaging agent which may be used for gated blood pool imaging and for the detection of sites of gastrointestinal bleeding. When reconstituted with sterile non-pyrogenic isotonic saline and administered intravenously 30 minutes prior to the intravenous administration of Sodium Pertechnetate Tc 99m Injection, approximately 76% of the injected radioactivity remains in the blood pool.

CONTRAINDICATIONS

None known.

WARNINGS

As an adjunct in the diagnosis of confirmed myocardial infarction (ECG and serum enzymes positive), the incidence of false negative images has been found to be 6 percent. False negative images can also occur if made prior to 24 hours in the evolutionary phase of the infarct or after 6 days in the resolution phase. In a limited study involving 22 patients in whom the ECG was positive and serum enzymes questionable or negative, but in whom the final diagnosis of acute myocardial infarction was made, the incidence of false negative images was 23 percent. The incidence of false positive images has been found to be 7 to 9 percent. False positive images have also been reported following coronary by-pass graft surgery, in unstable angina pectoris, old myocardial infarcts and in cardiac contusions.

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

The biodistribution of technetium Tc 99m pyrophosphate may be altered in the presence of high levels of certain cations (iron, calcium, and aluminum). This may result in reduced uptake of radionuclide in the skeleton and increased extraosseal uptake, which may potentially degrade imaging quality. High levels of these cations may be caused by concomitant medications or medical conditions (e.g., iron overload, hypercalcemia, etc.). Most cases were observed after iron infusion. (See **PRECAUTIONS, Drug Interactions**.)

PRECAUTIONS

General

The lyophilized contents of the Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection reaction vial are to be administered to the patient only as an intravenous solution (see Procedures for Reconstitution). Any Sodium Pertechnetate Tc 99m solution which contains an oxidizing agent is not suitable for use with Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection. When reconstituted with Sodium Pertechnetate Tc 99m, Technetium Tc 99m Pyrophosphate Injection must be used within 6 hours. Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection may also be reconstituted with sterile, non-pyrogenic isotonic saline containing no preservatives and injected intravenously prior to the administration of

Sodium Pertechnetate Tc 99m Injection.

Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection contains no preservatives. Vials are sealed under nitrogen: air or oxygen is harmful to the contents of the vials and the vials should not be vented.

The components of the Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection are supplied sterile and non-pyrogenic. Aseptic procedures normally employed in making additions and withdrawals for sterile, non-pyrogenic containers should be used during addition of the Sodium Pertechnetate Tc 99m Injection and the withdrawal of doses for patient administration.

Shielding should be utilized when preparing Technetium Tc 99m Pyrophosphate Injection.

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

The solution should not be used if cloudy, discolored, or found to contain particulate matter.

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.

No special handling is required for the non-radioactive drug product.

Bone Imaging

Both prior to and following Technetium Tc 99m Pyrophosphate Injection administration, if not contraindicated for the patient's cardiac condition, patients should be encouraged to drink fluids. Patients should void as often as possible after the Technetium Tc 99m Pyrophosphate Injection to minimize background interference and unnecessary radiation exposure from accumulation in the bladder.

Cardiac Imaging

Patient's cardiac condition should be stable before beginning the cardiac imaging procedure.

Interference from chest wall lesions such as breast tumors and healing rib fractures can be minimized by employing the three recommended projections. (See **DOSAGE AND ADMINISTRATION**). False-positive and false-negative myocardial scans may occur; therefore, the diagnosis of acute myocardial infarction depends on the overall assessment of laboratory and clinical findings.

Blood Pool Imaging

The non-radioactive reconstituted agent should be injected by direct venipuncture. Heparinized catheter systems should be avoided, as interference with red blood cell tagging will result. Cardiac pool imaging should be initiated 15 to 30 minutes after the administration of Sodium Pertechnetate Tc 99m Injection.

The imaging of gastrointestinal bleeding is dependent on such factors as the region of imaging, rate and volume of the bleed, efficacy of the labeling of the red blood cells and timeliness of imaging. Due to these factors, images should be taken sequentially over a period of time until a positive image is obtained or clinical conditions warrant the discontinuance of the procedure. The period of time for collecting the images may range up to 36 hours.

Technetium Tc 99m Pyrophosphate Injection and the non-radioactive reconstituted Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection should be formulated within six (6) hours prior to clinical use.

Drug Interactions

The biodistribution of technetium Tc 99m pyrophosphate may be altered in the presence of high levels of certain cations (iron, calcium, and aluminum). This may result in reduced uptake of radionuclide in the skeleton and increased extraosseal uptake, which may potentially degrade imaging quality. In patients with high levels of these cations caused by concomitant medications, particularly patients receiving iron infusions, consider performing an imaging study with technetium Tc 99m pyrophosphate injection once the cation levels have normalized (e.g., after 3 to 5 half-lives of the cation). (See **WARNINGS**.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Pyrophosphate Injection. It is also not known whether Technetium Tc 99 Pyrophosphate Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc 99m Pyrophosphate Injection should be given to a pregnant woman only if clearly needed.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, to 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 Pyrophosphate Injection is excreted in human milk during lactation, therefore, formula feeding should be substituted for breast feeding.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of the Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Some hypersensitivity reactions have been associated with pyrophosphate use.

DOSAGE AND ADMINISTRATION

After preparation with oxidant-free Sodium Pertechnetate Tc 99m Injection, the suggested dose range of Technetium Tc 99m Pyrophosphate Injection in the average ADULT patient (70 kg) is:

Bone Imaging - 185-555 megabecquerels (5-15 mCi)

Cardiac Imaging - 370-555 megabecquerels (10-15 mCi)

The suggested dose range of the non-radioactive reconstituted Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection in the average ADULT patient (70 kg) is:

Blood Imaging - Administer not less than one-third nor more than the total contents of one vial. [555-740 megabecquerels (15-20mCi) of Pertechnetate Tc 99m Injection].

Bone and Cardiac Imaging

Technetium Tc 99m Pyrophosphate Injection is injected intravenously over a 10 to 20 second period. For optimal results, bone imaging should be done 1 to 6 hours following administration. Cardiac imaging should be done 30 to 90 minutes following administration. The acute myocardial infarct can be visualized from 24 hours to 6 days following onset of symptoms, with maximum localization at 48 to 72 hours. Cardiac imaging should be done with a gamma scintillation camera. It is recommended that images be made of the anterior, left anterior oblique and left lateral projections.

Blood Pool Imaging

Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection may be reconstituted with sterile, non-pyrogenic isotonic saline containing no preservatives. Administer not less than one-third nor more than the total contents of one vial 30 minutes prior to the intravenous administration of 555 to 740 megabecquerels (15-20 mCi) Sodium Pertechnetate Tc 99m Injection. The non-radioactive reconstituted Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection should be injected by direct venipuncture. Heparinized catheter systems should be avoided. Cardiac imaging should be done 10 to 30 minutes following the administration of Sodium Pertechnetate Tc 99m Injection utilizing a scintillation camera interfaced to an electrocardiographic gating device.

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

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

Radiation Dosimetry

Bone and Cardiac Imaging

The effective half-life was assumed to be the physical half-life for all calculated values. The estimated radiation absorbed doses to an average ADULT patient (70 kg) from an intravenous injection of a maximum of 555 megabecquerels (15 mCi) of Technetium Tc 99m Pyrophosphate Injection are shown in Table 4.

Table 4. Estimated Absorbed Radiation Doses
Bone and Cardiac Imaging*

	Technetium Tc 99m Pyrophosphate Injection	
Target Organ	**mGy/555 MBq**	**rads/15 mCi**
Total Body	1.8	0.18
Kidneys	3.6	0.36
Red Marrow	3.5	0.35

Bone Surfaces	21.1	2.11
Bladder Wall	13.3	1.33
Testes	1.4	0.14
Ovaries	2.1	0.21
Effective Dose Equivalent	3.3 mSv	0.33 rem

*Based on the model in MIRD Dose Estimate Report No. 13 (J Nucl Med 30:1117- 1122, 1989).

Estimate calculated using phantoms of Cristy & Eckerman (Report ORNL/TM-8381/V1 & V7). Bone and marrow model of Eckerman (Aspects of dosimetry of radionuclides within the skeleton with particular emphasis on the active marrow. In Fourth International Radiopharmaceutical Dosimetry Symposium; A.T. Schlafke-Stelson and E.E. Watson eds. CONF-851113, Oak Ridge Associated Universities, Oak Ridge, TN 37831, 1986. pp 514-534.) used.

The effective dose equivalent is a quantity which may be suitable for comparing risks of different procedures in nuclear medicine, radiology, and other applications involving ionizing radiation, but should not be construed to give information about risks to individual patients and should not be applied to situations involving radiation therapy.

Blood Pool Imaging

The estimated absorbed radiation doses to an average adult patient (70 kg) from an intravenous injection of 740 megabecquerels (20 mCi) of Sodium Pertechnetate Tc 99m Injection, 30 minutes after the intravenous administration of the non-radioactive reconstituted Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection are shown in Table 5.

Table 5. Estimated Absorbed Radiation Doses Blood Pool Imaging[a]

Sodium Pertechnetate Tc 99m 30 min. Post Injection with Pyrophosphate Target Organ	mGy/740 MBq	rads/20 mCi
Total Body	3.2	0.32
Spleen	3.6	0.36
Bladder Wall[b]	24.0	2.40
Testes	2.4	0.24
Ovaries	4.6	0.46
Blood	10.4	1.04
Red Marrow	4.4	0.44

[a] Assume 75% of the Sodium Pertechnetate Tc 99m labels red blood cells and the other 25% remains as pertechnetate. Method of calculation: MIRD Dose Estimate Report No. 8, ***J Nucl Med*** 17:74-77,1976.

[b] If 25% excreted with 1 hour T_b

HOW SUPPLIED

The Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection is supplied in packages of 5 or 30 sterile, non-pyrogenic, white-capped 10mL vials.

Each multidose vial contains 12.0 mg sodium pyrophosphate, 2.8 mg minimum stannous tin as

stannous chloride dihydrate and 4.9 mg maximum total tin as stannous chloride dihydrate; pH is adjusted with hydrochloric acid to 5.3-5.7 prior to lyophilization. No bacteriostatic preservative is present. Sealed under nitrogen. Included in each 5-vial package are one package insert and 10 radiation labels. Included in each 30-vial package are one package insert and 60 radiation labels.

Store the kit as packaged at 20-25°C (68-77°F) [See USP]. Store the reconstituted vials at 20-25°C (68-77°) [See USP].

Directions for use

Bone and Cardiac Imaging

Technetium Tc 99m Pyrophosphate Injection is prepared from the Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection by the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure. Remove the white flip-off cap from the vial and swab the top of the vial closure with alcohol to sterilize the surface.
2. Complete the radiation label and affix to the vial. Place the vial in an appropriate radiation shield suitably labeled and identified.
3. With a sterile shielded syringe, aseptically obtain 1-10 milliliters of a suitable, oxidant free, sterile and non-pyrogenic Sodium Pertechnetate Tc 99m Injection containing no more than 3.7 gigabecquerels (100 mCi). Aseptically add the Sodium Pertechnetate Tc 99m Injection to the vial
4. Swirl the contents of the vial for one minute and let stand for at least 10 minutes.
5. Record date and time of preparation.
6. It is recommended that the radiochemical purity of the prepared radiopharmaceutical be checked prior to patient administration.
7. Examine vial contents for particulates and discoloration prior to injection.
8. Withdrawals for administration must be made aseptically using a sterile shielded syringe and needle. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be vented. If repeated withdrawals are made from a vial, the replacement of contents with air should be minimized.
9. Aseptically withdraw material with a sterile lead shielded syringe for use within six (6) hours of preparation. For optimal results, this time should be minimized. The vial contains no bacteriostatic preservative. Store the reconstituted vial at 20-25°C (68-77°F) [See USP]. Discard the vial six (6) hours after reconstitution.
10. The patient dose should be measured by suitable radioactivity calibration system immediately prior to administration.

Blood Pool Imaging

The non-radioactive Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection is prepared by adhering to the following aseptic procedure:

1. Remove the white flip-off cap from the vial and swab the top of the vial closure with alcohol to sterilize the surface.
2. Reconstitute the reaction vial with 3 milliliters of sterile, non-pyrogenic, isotonic saline containing no preservatives.
3. Swirl the contents of the vial for one minute and let stand for at least 10 minutes.
4. Record date and time of preparation.
5. Examine vial contents for particulates and discoloration prior to injection.
6. Withdrawals for administration must be made aseptically using a sterile syringe and needle. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be

vented. If repeated withdrawals are made from a vial, the replacement of contents with air should be minimized.

7. Aseptically withdraw the reconstituted non-radioactive Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection with a sterile syringe for use within six (6) hours of preparation. For optimal results, this time should be minimized. The vial contains no bacteriostatic preservative. Store the reconstituted vial at 20-25°C (68-77°F) [See USP]. Discard the vial six (6) hours after reconstitution.
8. Between one-third and a total vial of stannous pyrophosphate may be administered by direct venipuncture 30 minutes prior to intravenous administration of 555 to 740 megabecquerels (15-20 mCi) of Sodium Pertechnetate Tc 99m Injection. Heparinized catheter systems should not be used.
9. The patient dose of Sodium Pertechnetate Tc 99m Injection should be measured by a suitable radioactivity calibration system immediately prior to administration.

NDC # 45567-0060-1 for 5 vial kits

NDC # 45567-0060-2 for 30 vial kits

This reagent kit for preparation of a radiopharmaceutical is approved for use by persons licensed pursuant to Section 120.547, Code of Massachusetts Regulation 105, or under equivalent license of the U.S. Nuclear Regulatory Commission or an Agreement State.

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