PRODUCT MONOGRAPH

Kit for the Preparation of Technetium (^{99m}Tc) Pyrophosphate Injection

Lyophilized Powder for Solution, 12 mg

For intravenous administration

Diagnostic Radiopharmaceutical

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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

After reconstitution with saline, stannous pyrophosphate is indicated as an adjunct to sodium pertechnetate (^{99m}Tc):

- as a blood pool imaging agent which may be used for gated blood pool imaging; and
- for the detection of sites of gastrointestinal bleeding.

After reconstitution with sodium pertechnetate (^{99m}Tc), technetium (^{99m}Tc) pyrophosphate is indicated:

- for the detection of areas of altered osteogenesis;
- as an adjunct in the diagnosis of confirmed myocardial infarction (ECG and serum enzymes positive).

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (< 18 years of age).

1.2 Geriatrics

Geriatrics (> 65 years of age): there are no known limitations in geriatric patients.

2. CONTRAINDICATIONS

None known.

3. SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Both prior to and following administration of technetium (^{99m}Tc) pyrophosphate, patients should be encouraged to drink fluids. Patients should void as often as possible after administration to minimize background interference from its accumulation in the bladder and to reduce unnecessary exposure to radiation.

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

4.2 Dosage

The recommended amount of radioactivity to be administered is:

Skeletal imaging: 185 to 555 MBq

Cardiac imaging: 370 to 555 MBq

Blood pool imaging: One third of a vial of stannous pyrophosphate (*i.e,* 4 mg) followed by 555 to 740 MBq of sodium pertechnetate (^{99m}Tc) (see 4.3 *Administration*).

4.3 Administration

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if contents are turbid.

Prior to injection, verify the injected radioactivity by measuring the radioactivity of the vial with a dose calibrator.

Bone and Cardiac Imaging

Technetium (^{99m}Tc) pyrophosphate injection is injected intravenously over 10 to 20 seconds.

Blood Pool Imaging

In Vivo Method

Stannous pyrophosphate is administered intravenously 15 to 30 minutes prior to the intravenous administration of sodium pertechnetate (^{99m}Tc). Contents of the reconstituted kit should be injected by direct venipuncture. Heparinized catheter systems should be avoided.

Modified *In Vivo/In Vitro* Method using acid-citrate-dextrose (ACD)

An infusion set fitted with at 3-way stopcock is placed in a large peripheral vein. The line is kept patent with a continuous drip of sterile, non-pyrogenic normal saline containing no preservatives.

Thirty minutes after the injection of stannous pyrophosphate, the infusion line and stopcock are cleared by withdrawing and discarding approximately 5 mL of whole blood. Immediately following, approximately 5 mL of whole blood are withdrawn into a syringe containing 1 mL preservative-free acid-citrate-dextrose (ACD) and 555 to 740 MBq of sodium pertechnetate (^{99m}Tc). The stopcock is then turned, residual blood is flushed from the intravenous line, and the normal saline flow is readjusted.

The syringe is gently rotated to mix and allowed to incubate at room temperature for 10 minutes prior to injection via the 3-way stopcock.

Modified *In Vivo/In Vitro Method* using heparin

An infusion set fitted with at 3-way stopcock is placed in a large peripheral vein. The line is kept patent with a saline solution containing 5-10 units per mL of preservative-free heparin.

Thirty minutes after the injection of stannous pyrophosphate, 3 mL of blood are withdrawn into a syringe containing 555 to 740 MBq of sodium pertechnetate (^{99m}Tc).

The syringe is gently rotated to mix and allowed to incubate at room temperature for 10 minutes prior to injection via the 3-way stopcock.

4.4 Image Acquisition and Interpretation

Bone and Cardiac Imaging

For optimal results, bone imaging should be done one to six hour following administration.

Cardiac imaging should be done 60 to 90 minutes following administration. The acute myocardial infarct can be visualized from 24 hours to nine days following onset of symptoms, with maximum localization at 48 to 72 hours.

It is recommended that images be made of the anterior, left anterior oblique and left lateral projections.

Blood Pool Imaging

Cardiac imaging should be done 10 minutes following the administration of sodium pertechnetate (^{99m}Tc) (*in vivo* method) or ^{99m}Tc-labeled red blood cells (modified *in vivo/in vitro* method).

Gastrointestinal bleeding

The imaging of gastrointestinal bleeding is dependent on such factors as the region of imaging, rate and volume of the bleed, efficacy of 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 thirty-six hours.

4.5 Instructions for Preparation and Use

Drug Preparation

The components of the reagent vial are sterile and non-pyrogenic. It is essential that the user uses strict aseptic techniques.

Waterproof gloves should be worn during the entire preparation and dispensing procedure.

All transfers of sodium pertechnetate (^{99m}Tc) and of technetium (^{99m}Tc) pyrophosphate should be done with an adequately shielded syringe and aseptic technique.

Any sodium pertechnetate (^{99m}Tc) which contains an oxidizing agent is not suitable for use in the preparation of technetium (^{99m}Tc) pyrophosphate injection.

Technetium (^{99m}Tc) pyrophosphate should be kept in a capped lead shield for the duration of its 6-h shelf-life.

Bone and Cardiac Imaging

1. Label the reaction vial and place the vial in a lead dispensing shield fitted with a lead cap and having a minimum wall thickness of 1/8 inch. Do not remove the vial from the dispensing shield except temporarily for Step 5 below.
2. Add sodium pertechnetate (^{99m}Tc) solution (1 to 10 mL) to the reaction Vial. In choosing the amount of pertechnetate (^{99m}Tc) radioactivity to be used in the preparation of technetium (^{99m}Tc) pyrophosphate injection, the labeling efficiency, number of patients, administered radioactive dose and radioactive decay must be taken into account. The recommended maximum amount of pertechnetate (^{99m}Tc) to be added to the reaction vial is 3.7 GBq.
3. With the reaction vial in the dispensing shield (with cap in place), shake sufficiently to bring the lyophilized material into solution. Allow to stand for five (5) minutes at room temperature.
4. Using proper shielding, visually inspect the reaction vial. The resulting solution should be clear and free of particulate matter. If not, the vial should not be used.

5. Assay technetium (^{99m}Tc) pyrophosphate injection in a suitable calibrator and record the time, date of preparation and the activity onto the label.

Blood Pool Imaging

1. Reconstitute the vial with 3 mL of sterile, non-pyrogenic normal saline containing no preservatives.
2. Shake the vial sufficiently to bring the lyophilized material into solution. Allow to stand for five (5) minutes at room temperature.
3. Visually inspect the reaction vial. The resulting solution should be clear and free of particulate matter. If not, the vial should not be used.

4.6 Directions for Quality Control

The radiochemical purity of the radiopharmaceutical product should be determined prior to administration to the patient.

5 RADIATION DOSIMETRY

The effective dose following intravenous administration of 500 MBq for bone or cardiac imaging is 2.5 mSv. The critical organ is the urinary bladder (5.5E-02 mGy/MBq).

The effective dose following the administration of 700 MBq of sodium pertechnetate (^{99m}Tc) for blood pool imaging is 3.3 mSv. The critical organ is the urinary bladder (1.2E-02 mGy/MBq).

Table 1. Absorbed dose per unit activity administered (mGy/MBq)

Organ	Absorbed dose coefficient Cardiac/Bone imaging	Absorbed dose coefficient Blood pool imaging
Adrenals	3.09E-03	5.51E-03
Brain	1.88E-03	3.97E-03
Breasts	8.93E-04	3.69E-03
Esophagus	1.51E-03	4.39E-03
Eyes	1.88E-03	3.97E-03
Gallbladder Wall	1.77E-03	5.77E-03
Left colon	2.35E-03	5.65E-03
Small Intestine	2.76E-03	5.64E-03
Stomach Wall	1.34E-03	5.17E-03
Right colon	1.86E-03	5.61E-03
Rectum	8.17E-03	6.28E-03
Heart Wall	1.40E-03	5.24E-03
Kidneys	8.17E-03	5.41E-03
Liver	1.51E-03	5.06E-03
Lungs	1.46E-03	4.73E-03
Ovaries	5.63E-03	6.69E-03
Pancreas	1.85E-03	5.80E-03
Prostate	6.81E-03	5.48E-03
Salivary Glands	1.43E-03	4.39E-03
Red Marrow	6.41E-03	4.40E-03
Osteogenic Cells	4.10E-02	7.59E-03
Spleen	1.79E-03	5.05E-03
Testes	2.17E-03	3.89E-03
Thymus	1.19E-03	4.70E-03
Thyroid	1.44E-03	4.39E-03
Urinary Bladder Wall	5.54E-02	1.19E-02
Uterus	1.09E-02	7.17E-03
Total Body	3.03E-03	4.56E-03
Effective Dose (mSv/MBq)	**5.03E-03**	**4.67E-03**

From Stabin MG, Siegel JA. RADAR Dose Estimate Report: A Compendium of Radiopharmaceutical Dose Estimates Based on OLINDA/EXM Version 2.0. J Nucl Med. 2018;59(1):154-160.

Biokinetic data : ICRP 128 recommended model
Physical models : RADAR ICRP 89 Reference Phantom Series
Absorbed dose coefficients : OLINDA/EXM Version 2.0
Effective doses : ICRP 103 weighting factors
Sex averaged : ICRP 103

Estimates of fetal radiation doses are given in Table 2.

Table 2: Fetal Absorbed Radiation Doses

Indication	Early pregnancy	3-mo gestation	6-mo gestation	9-mo gestation
Cardiac/bone	8.1E-3	9.1 E-3	2.6 E-3	2.1E-3
Blood pool (*in vivo*)	7.0 E-3	5.5 E-3	2.2 E-3	8.7 E-4

From: Stabin MG. New-Generation Fetal Dose Estimates for Radiopharmaceuticals. J Nucl Med. 2018;59(6):1005-1006

6 OVERDOSAGE

Cases of overdose are not known to have occurred with technetium (^{99m}Tc) pyrophosphate Injection. In case of overdose, elimination should be encouraged by means of increased fluid intake and frequent urination.

7. DOSAGE FORMS, COMPOSITION AND PACKAGING

The kit for the preparation for the preparation of technetium (^{99m}Tc) pyrophosphate injection is supplied as a lyophilized powder in 10 mL vials. Each vial contains 10.8 to 13.2 mg sodium pyrophosphate, 2.8 mg (minimum) stannous chloride ($SnCl_2$•$2H_20$) and 3.6 to 4.9 mg total tin expressed as stannous chloride ($SnCl_2$•$2H_20$), sealed under an atmosphere of nitrogen. The pH of the reconstituted drug is between 5.0 and 6.0.

8. DESCRIPTION

8.1 Physical Characteristics

^{99m}Tc decays by isomeric transition to ^{99}Tc with a half-life of 6 hours. The principle (89%) emission has a mean energy of 140.5 keV.

To correct for the physical decay of this radionuclide, the activity remaining at any time point (in minutes from calibration) can be calculated using the following equation:

$$Activity\ at\ time\ t\ (in\ minutes\ from\ calibration) = Activity\ at\ calibration * e^{(-0.00192*t)}$$

Table 3: Physical Decay

Hours	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
Percent remaining	94.4	89.1	84.1	79.4	75.0	70.8	66.8	63.0	59.5	56.2	53.0	50.1

8.2 External Radiation

The specific γ-ray constant for ^{99m}Tc is 5.4 µC kg^{-1} MBq^{-1} h^{-1} at 1 cm.

Lead shielding attenuation coefficients for various lead thicknesses are shown in Table 4. For example, a 1.8 mm thick lead shield has a coefficient of attenuation of 0.01 and will decrease the external radiation by 99%.

Table 4. Radiation Attenuation of 140 keV Photons by Lead Shielding

	Lead Shield thickness (mm)			
	0.23	0.9	1.8	2.7
Coefficient of Attenuation	0.5	0.1	0.01	0.001

From: Smith DS, Stabin MG. Exposure rate constants and lead shielding values for over 1,100 radionuclides. Health Phys. 2012 102(3):271-91.

9. WARNINGS AND PRECAUTIONS

9.1 General

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

9.2 Cardiovascular

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

If not contraindicated by the cardiac status, patients should be encouraged to ingest fluids and to void frequently in order to reduce unnecessary radiation exposure.

Interference from chest wall lesions such as breast tumors and healing rib fractures can be minimized by employing the three recommended projections.

9.3 Contamination

A toilet rather than a portable urinal should be used for up to 12 hours after receiving the radiopharmaceutical product; the toilet should be flushed several times after use.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

9.4 Radiation Risk

Technetium (^{99m}Tc) contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. To reduce radiation exposure, ensure patients are well hydrated prior to administration of technetium (^{99m}Tc) pyrophosphate and advise patients to drink and void frequently during the first hours following administration.

9.5 Risk for Image Misinterpretation

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 too early in the evolutionary phase of the infarct or too late 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 been reported following coronary by-pass graft surgery, in unstable angina pectoris, old myocardial infarcts and in cardiac contusions.

9.6 Special Populations

Pregnant Women: 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.

Animal reproduction studies have not been conducted with technetium (^{99m}Tc) pyrophosphate injection. It is also not known whether this drug can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Technetium (^{99m}Tc) pyrophosphate injection should be given to a pregnant woman only if clearly needed.

Nursing Women: Technetium (^{99m}Tc) pyrophosphate is excreted in human milk during lactation. A child should not be breast fed until the radiopharmaceutical is no longer secreted in an amount estimated to give an effective dose >1 mSv to the child. As with most ^{99m}Tc-labelled compounds, under the circumstance that no free pertechnetate exists, no interruption in breast feeding is necessary in order to reach this limit following the administration of technetium (^{99m}Tc) pyrophosphate. An interruption of 4 h during which one meal is discarded can be advised to be on the safe side.

Pediatrics: The safety and effectiveness in pediatric patients have not been established

Geriatrics: It is not known if there are differences in the efficacy or safety of technetium (^{99m}Tc) pyrophosphate between elderly and younger patients.

10. ADVERSE REACTIONS

No reports of adverse reactions to technetium (^{99m}Tc) pyrophosphate could be identified in the published literature.

The Pharmacopeia Committee of the Society of Nuclear Medicine has reported two cases of mild anaphylaxis.

Adverse reactions to radiopharmaceuticals are very rare, less than 1 in 100,000. When reported, they are often non-specific (*e.g.,* nausea, vomiting, erythema, flushing, dizziness, syncope, hypotension, breathing difficulties) and may be related to a vaso-vagal reaction to the injection and not specifically related to the drug.

11. DRUG INTERACTIONS

11.1 Drug-Drug Interactions

Preliminary reports indicate impairment of blood pool images in patients receiving sodium heparin for anticoagulant therapy. This is characterized by a reduction in the amount of injected radioactivity remaining in the blood pool.

Reports indicate impairment of brain images using sodium pertechnetate (^{99m}Tc), which have been preceded by a bone image. The impairment may result in false positive or false negatives. It is recommended, where feasible, that brain imaging precede bone imaging procedures.

11.2 Drug-Food Interactions

There are no known interactions.

11.3 Drug-Herb Interactions

There are no known interactions.

11.4 Drug-Laboratory Interactions

There are no known interactions.

11.5 Drug-Lifestyle Interactions

There are no known interactions.

12. ACTION AND CLINICAL PHARMACOLOGY

At the doses used, technetium pyrophosphate (^{99m}Tc), stannous pyrophosphate, sodium pertechnetate (^{99m}Tc), and radiolabelled red cells do not seem to have any pharmacodynamic activity.

When injected intravenously, technetium (^{99m}Tc) pyrophosphate has specific affinity for areas of altered osteogenesis. It is also concentrated in the injured myocardium, primarily in areas of irreversibly damaged myocardial cells.

One or two hours after intravenous injection of technetium (^{99m}Tc) pyrophosphate, an estimated 40 to 50 percent of the injected dose is 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.

Pyrophosphate also has an affinity for red blood cells. When administered 15 to 20 minutes prior to the intravenous administration of sodium pertechnetate (^{99m}Tc) (*in vivo* red blood cell labeling), approximately 75 percent of the injected radioactivity remains in the blood pool providing excellent images of the cardiac chambers. Comparable percentages of the injected radioactivity are obtained when the modified *in vivo/in vitro* red blood cell labeling method is used.

13. STORAGE AND STABILITY

The Kit for the Preparation of Technetium (^{99m}Tc) Pyrophosphate should be stored at 20 to 25 °C.

The reconstituted vial [whether reconstituted with sodium pertechnetate (^{99m}Tc) or with saline] should be stored at controlled room temperature, 20 to 25 °C, and used within six hours of preparation.

14. SPECIAL HANDLING INSTRUCTIONS

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

PART II: SCIENTIFIC INFORMATION

15 PHARMACEUTICAL INFORMATION

Drug Substance

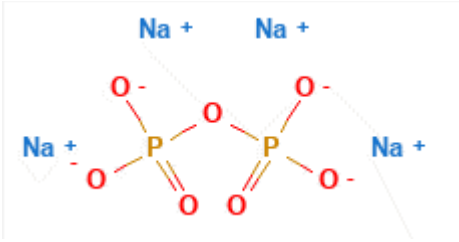
Proper name: Sodium pyrophosphate anhydrous

Tetrasodium pyrophosphate

Molecular formula: $Na_4P_2O_7$

Molecular weight: 265.9 g/mol

Structural formula:



Physico-chemical properties: Tetrasodium pyrophosphate appears as odorless, white powder or granules.

Melting point:	995°C
Density:	2.53 g/cm^3
Solubility in water:	3.16 g/100 mL (cold water); 40.26 g/100 mL boiling water.

16. CLINICAL TRIALS

No clinical studies have been conducted with Isologic's Kit for the Preparation of Technetium (^{99m}Tc) Pyrophosphate Injection.

17. NON-CLINICAL TOXICOLOGY

No data available.

18 SUPPORTING PRODUCT MONOGRAPHS

Technescan PYP Kit for the Preparation of Technetium Tc 99m Pyrophosphate Injection: Lyophilized Powder for Solution, 5 - 20 mCi. Submission control n°: 171131. Product Monograph. Mallinckrodt Canada ULC. March 13, 2014

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Kit for the preparation of technetium (^{99m}Tc) pyrophosphate injection

This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about this drug.

What the product used for?

Technetium (^{99m}Tc) pyrophosphate injection has a number of uses. Talk to your healthcare professional about the reasons for having prescribed this drug for you.

How does it work?

Technetium (^{99m}Tc) pyrophosphate gives off a small amount of radiation. Technetium (^{99m}Tc) pyrophosphate will accumulate in different parts of the body. A picture is taken with a gamma-camera. It shows how much of the drug is present in different parts of the body.

What are the ingredients?

The product contains technetium (^{99m}Tc) pyrophosphate and a small amount of stannous chloride (tin).

Technetium (^{99m}Tc) pyrophosphate injection comes in the following dosage forms:

Technetium (^{99m}Tc) pyrophosphate injection is only available as kit for intravenous injection.

What are possible side effects from using this product?

There are no known side effects.

If you want more information about technetium (^{99m}Tc) pyrophosphate injection:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php).

This leaflet was prepared by Isologic Innovative Radiopharmaceuticals Ltd.

Last Revised March 19, 2021