BRACCO DIAGNOSTICS

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PHOSPHOTEC®
Kit for the Preparation of Technetium Tc 99m Pyrophosphate

For Diagnostic Use

DESCRIPTION

Each reaction vial contains 40 mg sodium pyrophosphate (equivalent to 23.9 mg anhydrous sodium pyrophosphate) and 0.4 mg stannous fluoride (minimum) and 0.9 mg total tin (maximum) as stannous fluoride; the product does not contain a preservative. The pH of the product is adjusted with sodium hydroxide or hydrochloric acid prior to lyophilization. At the time of manufacture, the air in the vial Is replaced with a nitrogen gas atmosphere. The pH of the reconstituted product is 5.5 to 6.9. When sterile, nonpyrogenic sodium pertechnetate Tc 99m solution is added to the vial, a diagnostic agent, technetium Tc 99m pyrophosphate, is formed for intravenous administration; the structure of this radiolabeled complex is unknown. The product as supplied is sterile and nonpyrogenic.

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 shown in Table 1.

TABLE 1

Principal Radiation Emission Data		
Radiation	Mean % per 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 Tc 99m is 0.78 R/hour-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. To facilitate control of the radiation exposure amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of 1,000.

Table 2.

Radiation Attenuation by Lead Shielding	
Shield Thickness (Pb) cm	Attenuation Factor
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 technetium Tc 99m, 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	8	0.398
1	0.891	9	0.355
2	0.794	10	0.316
3	0.708	11	0.282
4	0.631	12	0.251
5	0.562	18	0.126
6	0.501	24	0.063
7	0.447		

*Calibration Time

CLINICAL PHARMACOLOGY

Bone and Cardiac Imaging

Following intravenous administration of the technetium Tc 99m pyrophosphate 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 bone. It is theorized that the complex also reacts with the mitochondrial calcium crystals, produced within infarcted myocardial cells which are believed to be hydroxyapatite; this phenomenon usually does not persist beyond six days after the occurrence of an infarction.

Clearance of the radioactivity from the blood is quite rapid with skeletal uptake and urinary excretion being the principal mechanisms of clearance. At two hours following intravenous injection, approximately 55 percent of the injected dose has localized in bone; at four hours approximately 10 percent of the dose remains in the vascular system, decreasing to about 7 percent at 24 hours. The average urinary excretion was observed to be about 38 percent of the administered dose after eight hours increasing to an average of about 44 percent at 24 hours. A minimum amount of uptake has been observed in soft-tissue organs, most notably the kidneys.

Blood Pool Imaging

The ***in vivo*** tagging of Phosphotec results in the radiolabelling of red blood cells. Approximately 76 percent of the injected activity remains in the blood pool between 30 and 60 minutes after injection of sodium pertechnetate Tc 99m, thereby permitting excellent images of the cardiac chambers.

Maximum blood radioactivity levels occur in about 30 minutes; the initial biological half-life is approximately 18 hours. There is virtually no biological elimination of the agent after approximately six hours.

INDICATIONS AND USAGE

Bone Imaging

Phosphotec (Kit for the Preparation of Technetium Tc 99m Pyrophosphate) may be used as a bone imaging agent to delineate areas of altered osteogenesis.

Cardiac Imaging

Phosphotec is a cardiac imaging agent used as an adjunct in the diagnosis of acute myocardial infarction. The infarction is best visualized one to six days after onset of symptoms. False-negative images can occur if imaging is done too early in the evolutionary phase of the infarct or too late in the resolution phase. The incidence of false-positives may range from 5 to 9 percent and of false-negatives from 6 to 9 percent but may vary even more depending on selection criteria of patient populations.

Blood Pool Imaging
Phosphotec is also a blood pool imaging agent which may be used for gated cardiac blood pool imaging and for the detection of sites of gastrointestinal bleeding. When administered intravenously 15 to 60 minutes prior to intravenous administration of sodium pertechnetate Tc 99m, approximately 75% of the injected activity remains in the blood pool.

CONTRAINDICATIONS
None known.

WARNINGS
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 may be employed.

PRECAUTIONS

General
The lyophilized contents of the Phosphotec reaction vial are to be administered to the patient only as an intravenous solution (see PROCEDURES FOR RECONSTITUTION OF PHOSPHOTEC).

Any sodium pertechnetate Tc 99m solution which contains an oxidizing agent is **not** suitable for use with Phosphotec (Kit for the Preparation of Technetium Tc 99m Pyrophosphate).

When reconstituted with sodium pertechnetate Tc 99m**,** Phosphotec must be used within 6 hours. When reconstituted with Sodium Chloride Injection USP for blood pool imaging, use the solution within 30 minutes.

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.

Technetium Tc 99m Pyrophosphate 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 occupational workers consistent with proper patient management.

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.

Bone Imaging
Both prior to and following administration of the technetium Tc 99m pyrophosphate, the patient should be encouraged to drink fluids and to void as often as possible thereafter to minimize radiation exposure to the bladder and background interference during imaging.

Cardiac Imaging
The patient's cardiac condition should be stable before beginning the cardiac imaging procedure. If not contraindicated by the patient's cardiac status, patients should be encouraged to drink fluids and to void as often as possible in order to reduce unnecessary radiation exposure to the bladder. 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 reconstituted agent should be injected by direct venipuncture. Heparinized catheter systems should be avoided, as interference with red blood cell tagging will result.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed to determine any carcinogenic potential or impairment of fertility in males or females,

Teratogenic Effects: Pregnancy Category C
Animal reproduction studies have not been conducted with technetium Tc 99m pyrophosphate. It is also not known whether technetium Tc 99m pyrophosphate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Technetium Tc 99m pyrophosphate should be administered to a pregnant woman only if clearly needed.

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

Nursing Mothers
Caution should be exercised when technetium Tc 99m pyrophosphate is administered to a nursing woman. Technetium Tc 99m is excreted in human milk during lactation; therefore, formula-feedings should be substituted for breast-feedings.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Several adverse reactions due to Phosphotec have been reported. These were usually hypersensitivity reactions characterized by itching, various skin rashes, hypotension, fever, chills, nausea, vomiting and dizziness.

DOSAGE AND ADMINISTRATION

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

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

Intravenous doses for an average adult (70 kg) are as follows:

Bone Imaging
The suggested dose is 370 to 555 MBq (10 to 15 mCi).

Following reconstitution, Phosphotec is injected intravenously over a 10- to 20-second period. Imaging may be started at one hour after administration; however, for optimal results bone imaging should be performed two to four hours following administration.

Cardiac Imaging
The suggested dose is 370 to 555 MBq (10 to 15 mCi) administered intravenously over 10 to 20 seconds and within 24 hours to six days after the onset of symptoms suggestive of acute myocardial infarction.

Imaging is recommended at 45 to 60 minutes postinjection. It is suggested that scans be obtained in at least three projections (e.g., anterior, lateral, and left anterior oblique).

Blood Pool Imaging
The suggested dose is 41 mg (contents of one reaction vial) of Phosphotec (Kit for the Preparation of Technetium Tc 99m Pyrophosphate) (see PROCEDURE FOR RECONSTITUTION) administered intravenously, followed 15 to 60 minutes later by the intravenous administration of 740 MBq (20 mCi) of sodium pertechnetate Tc 99m. Administration should be made by direct venipuncture and not by heparinized catheter systems. Cardiac pool imaging should be initiated 15 to 30 minutes after the administration of sodium pertechnetate Tc 99m.

Radiation Dosimetry
The effective half-life was assumed to be equal to the physical half-life for all calculated values. The estimated absorbed radiation doses to an average adult (70 kg) from an intravenous injection are shown in Tables 4 and 5.

TABLE 4 Bone and Cardiac Imaging

Estimated Absorbed Radiation Doses		
Technetium Tc 99m Sodium Pyrophosphate		
Target Organ	mGy/555 MBq	rads/15 mCi
Total Body[+]	2.3	0.23
Kidneys	7.1	0.71
Bone Marrow	5.7	0.57
Skeleton*	8.1	0.81
Bladder Wall		
2 hour void	14.6	1.46
4.8 hour void	34.5	3.45
Testes		
2 hour void	1.5	0.15
4.8 hour void	2.3	0.23
Ovaries		
2 hour void	1.4	0.14
4.8 hour void	2.3	0.23

[+]If patient voids frequently after radiopharmaceutical is administered, this dose will be reduced slightly.

*Dose at point of highest uptake may be a factor of 10 higher.

TABLE 5

lood Pool Imaging*

Estimated Absorbed Radiation Doses		
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†	24	2.4
Testes	2.4	0.24
Ovaries	4.6	0.46
Blood	10.4	1.04

[*]Assume 75% of the Sodium Pertechnetate Tc 99m labels red blood cells and the other 25% remains as pertechnetate.

[†]If 25% excreted with 1 hour T_b.

Method of Calculation: MIRD Dose Estimate Report No. 8, J Nucl Med 17:74-77, 1976.

HOW SUPPLIED

Phosphotec (Kit for the Preparation of Technetium Tc 99m Pyrophosphate) is supplied in a kit containing 10 reaction vials (5 mL size), 10 pressure-sensitive labels, and 1 package insert.

Storage

Store the Phosphotec (Kit for the Preparation of Technetium Tc 99m Pyrophosphate) refrigerated at 2°-8°C (36°-46°F). The reconstituted preparation should be refrigerated since the product does not contain a preservative. When reconstituted with sodium pertechnetate Tc 99m, Phosphotec must be used within 6 hours. When reconstituted with Sodium Chloride Injection USP for blood pool imaging, use the solution within 30 minutes.

PROCEDURES FOR RECONSTITUTION OF PHOSPHOTEC

Procedural Precautions

The contents of the Phosphotec reaction vial are sterile and nonpyrogenic. Aseptic procedures should be used during reconstitution of Phosphotec and the withdrawal of doses for intravenous administration. The introduction of air into the vial during the reconstitution step should be avoided.

Reconstitution Bone and Cardiac Imaging

Technetium Tc 99m pyrophosphate must be used within 6 hours.

1. Waterproof gloves Should be worn during the preparation procedure.
2. Allow the contents of the reaction vial to come to room temperature.
3. Place reaction vial in an appropriate lead shield with a fitted cover.
4. Swab the rubber closure of the reaction vial with a germicide.
5. Using a shielded syringe, slowly inject 2 to 4 mL [up to 2775 MBq (75 mCi)] of sterile sodium pertechnetate Tc99m solution into the reaction vial. In determining the amount of technetium Tc 99m radioactivity to be used, the labeling efficiency, number of patients, administered radioactive dose and radioactive decay must be taken into account. **NOTE:** If sodium pertechnetate Tc 99m solution must be diluted for use with Phosphotec (Kit for the Preparation of Technetium Tc 99m Pyrophosphate), only Sodium Chloride Injection USP (without preservatives) should be used.
6. Secure the lead shield cover. Shake the vial gently to bring the lyophilized material into solution.
7. Record the time and date of preparation and the radioconcentration and volume of the solution on the pressure-sensitive label.
8. Affix the pressure-sensitive label to the shield.
9. Using proper shielding, examine vial contents. If the solution is not clear and free of particulate matter and discoloration on visual inspection, it should not be used.
10. Maintain adequate shielding of the radioactive preparation including the use of appropriate shielded syringes.
11. Radioassay of technetium Tc 99m pyrophosphate may be accomplished conveniently by using an ionization chamber-type dose calibrator.

Blood Pool Imaging

When reconstituted with Sodium Chloride Injection USP, Phosphotec should be used within 30 minutes.

1. Allow the contents of the reaction vial to come to room temperature. Swab the top of the rubber closure with a germicide.
2. Slowly inject 2 to 5 mL Sodium Chloride Injection USP (without preservatives) into the reaction vial.
3. Shake the vial gently to bring the lyophilized material into solution.
4. If the solution is not clear and free of particulate matter and discoloration on visual inspection it should not be used

The U.S. Nuclear Regulatory Commission has approved this reagent kit for distribution to persons licensed to use byproduct material identified in §35.200 of 10 CFR Part 35, to persons who hold an equivalent license issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

Rx only
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