MYOVIEW24™ N176A

24 Hour Expiration

Kit for the Preparation of Technetium Tc99m Tetrofosmin for Injection
Stabilized with ascorbic acid, sodium hydrosulfite, and parabens

Diagnostic Radiopharmaceutical
For intravenous use only
Rx ONLY
NOT FOR USE IN NEWBORNS (contains preservatives)
CONTAINS SODIUM HYDROSULFITE

DESCRIPTION

The MYOVIEW24™ kit is supplied as a pack of five vials each of:

- MYOVIEW™ (Drug Substance)
- Bacteriostatic Sodium Chloride Injection, USP, 0.9% (10 mL and 30 mL; Antimicrobial Preservative), and,
- five ampules of Ascorbic Acid Injection, USP, 1 mL (Radioprotectant, containing sodium hydrosulfite).

When reconstituted and stored according to the prescribed instructions, MYOVIEW24 can be used for up to 24 hours after reconstitution. See INSTRUCTION FOR THE PREPARATION OF MYOVIEW24, the preparation of ~~a~~ technetium Tc99m tetrofosmin intravenous injection to be used for the scintigraphic delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium. Each MYOVIEW vial contains a predispensed, sterile, non-pyrogenic, lyophilized mixture of 0.23 mg tetrofosmin [6,9-bis(2-ethoxyethyl)-3,12-dioxa-6,9-diphosphatetradecane], 30 µg stannous chloride dihydrate (minimum stannous tin 5.0 µg; maximum total stannous and stannic tin 15.8 µg), 0.32 mg disodium sulphosalicylate and 1.0 mg sodium D-gluconate, and 1.8 mg sodium hydrogen carbonate. The lyophilized powder is sealed under a nitrogen atmosphere with a rubber closure and contains no antimicrobial preservative.

The structural formula of tetrofosmin is:

(CHEMICAL STRUCTURE)

$C_{18}H_{40}O_4P_2$

When sterile, pyrogen-free sodium pertechnetate Tc99m in isotonic saline is added to the vial, a Tc99m complex of tetrofosmin is formed.

Administration is by intravenous injection for diagnostic use.

Physical Characteristics

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.03 hours[(1)]. Photons that are useful for imaging studies are listed in Table 1.

Table 1
Principal radiation emission data - technetium Tc99m

Radiation	Mean % /disintegration	Mean energy (keV)
Gamma 2	87.87	140.5

1) Dillman, L.T. and Von der Lage, F.C. Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation. MIRD Pamphlet No. 10, P62,1975.

External Radiation
The specific gamma ray constant for technetium Tc99m is 206 microCoulomb.kg^{-1}/37 MBq-hr (0.8 R/mCi-hr) at 1 cm. The first half-value thickness of lead (Pb) for technetium Tc99m is 0.2mm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of Pb is shown in Table 2. For example, the use of a 2.7mm thickness of Pb will decrease the external radiation exposure by a factor of 1000.

Table 2
Radiation attenuation by lead shielding

Shield thickness (Pb) mm.	Coefficient of Attenuation
0.2	0.5
0.95	10^{-1}
1.8	10^{-2}
2.7	10^{-3}
3.6	10^{-4}
4.5	10^{-5}

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

Table 3
Physical decay chart - Tc99m half-life 6.03 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.399
2	0.795	9	0.355
3	0.708	10	0.317
4	0.631	11	0.282
5	0.563	12	0.252
6	0.502	24	0.063

*Calibration time (time of preparation)

CLINICAL PHARMACOLOGY

General
When technetium Tc99m pertechnetate is added to tetrofosmin in the presence of stannous reductant, a lipophilic, cationic technetium Tc99m complex is formed, Tc99m tetrofosmin. This complex is the active ingredient in the reconstituted drug product, on whose biodistribution and pharmacokinetic properties the indications for use depend.

Pharmacokinetics
Studies in normal volunteers have demonstrated rapid myocardial uptake of Tc99m tetrofosmin, and rapid blood, liver and lung clearances. Uptake in the myocardium reaches a maximum of about 1.2% of the injected dose (i.d.) at 5 minutes and approximately 1% of the i.d. at 2 hours, respectively. Background activities in the blood, liver and lung were less than 5% of the administered activity in whole blood at 10 minutes post-injection, less than 4.5% i.d., after 60 minutes, and less than 2% i.d. after 30 minutes. Approximately 66% of the injected activity is excreted within 48 hours post-injection, with approximately 40% excreted in the urine and 26% in the feces.
The kinetics, elimination and protein binding of Tc99m tetrofosmin have not been determined.

Pharmacodynamics
The pharmacodynamic cellular uptake of tetrofosmin in humans has not been established. In humans the recommended imaging time is 15 minutes at stress and 30 minutes at rest.

Metabolism
The metabolic profile of tetrofosmin has not been established.

Drug-Drug Interactions
Specific drug-drug interactions have not been studied.

Clinical Trials
A total of 252 patients with ischemic heart disease or atypical chest pain who had a reason for exercise stress imaging were studied in two open-label, multi-center, clinical trials of Tc99m tetrofosmin administered as Myoview™ (study a and study b). Of these 252 patients there were 212 (83%) males and 40 (17%) females with a mean age of 60.5 years (range 33.7 to 82.4 years). At peak exercise, maximum heart rate achieved and peak systolic blood pressure were comparable after MYOVIEW and thallium-201 exercise studies.

All patients had exercise and rest planar imaging with MYOVIEW and thallium-201; 191 (76%) patients also had SPECT imaging. The MYOVIEW and thallium-201 images were separated by a mean of 5.1 days (1-14 days before or 2-14 days after MYOVIEW). For MYOVIEW imaging, each patient received 185-296 MBq (5-8 mCi) Tc99m tetrofosmin at peak exercise and 555-888 MBq (15-24 mCi) Tc99m tetrofosmin at rest approximately 4 hours later. For thallium-201 imaging, patients received thallium-201 55.5-74 MBq (1.5-2.0 mCi) at peak exercise.

The images were evaluated for the quality of the image (excellent, good or poor) and the diagnosis (with scores of 0 = normal, 1 = ischemia, 2 = infarct, 3 = mixed infarct and ischemia). The primary outcome variable was the percentage of correct diagnoses in comparison to the final clinical diagnosis. All planar images were blindly read; SPECT images were evaluated by the unblinded investigator. A subset of 181/252 (71%) patients had coronary angiography comparisons to the planar images of MYOVIEW or thallium-201.

In comparison to the clinical diagnosis, results of MYOVIEW and thallium-201 imaging were comparable within the 95% confidence intervals. The results for each blinded reader are noted in the following table.

OVERALL DIAGNOSTIC OUTCOME

Total percentage correctly diagnosed	**Thallium-201**	**MYOVIEW™**
lschemia	Reader 1, Reader 2	Reader 1, Reader 2
Study a	77.7%,75.0%	66.3%,63.6%
Study b	75.6%,68.9%	66.4%,66.4%
Infarct		
Study a	75.9%,75.0%	75.9%,75,0%
Study b	70.6%,69.7%	73.1%, 68.1%

INDICATIONS AND USAGE

MYOVIEW24 is indicated for scintigraphic imaging of the myocardium following separate administrations under exercise and resting conditions. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium.

CONTRAINDICATIONS

None reported. (see WARNINGS)

WARNINGS

Contains sodium hydrosulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

In studying patients with known or suspected coronary artery disease, care should be taken to ensure continuous cardiac monitoring and the availability of emergency cardiac treatment.

The preservatives, propylparaben and methylparaben, are contained in the diluent (Bacteriostatic Sodium Chloride for Injection, USP, 0.9%) for this product. Data is unavailable on the toxicity of parabens and other preservatives in newborns. MYOVIEW24 is not for use in newborns (contains preservatives).

PRECAUTIONS

General

To minimize radiation dose to the bladder, the patient should be encouraged to void when the examination is completed and as often thereafter as possible. Adequate hydration should be encouraged to permit frequent voiding.

The contents of the MYOVIEW vial are intended only for use in the preparation of technetium Tc99m tetrofosmin injection and are NOT to be administered directly to the patient.

As with all injectable drug products, allergic reactions and anaphylaxis may occur.

Sometimes Tc99m labeled myocardial imaging agents may produce planar and SPECT images with different imaging information.

Technetium Tc99m tetrofosmin injection, like other radioactive drugs, must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to the patient consistent with proper patient management.

Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Drug Interactions: Drug interactions were not noted and were not studied in clinical studies in which MYOVIEW was administered to patients receiving concomitant medication. Drugs such as beta blockers, calcium blockers and nitrates may influence myocardial function and blood flow. The effects of such drugs on imaging results are not known.

The supplied Bacteriostatic Sodium Chloride Injection, USP, 0.9% and Ascorbic Acid Injection, USP are for use with the MYOVIEW24 kit only.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies have not been conducted to evaluate carcinogenic potential or effects on fertility. Tetrofosmin sulphosalicylate was not mutagenic *in vitro* in the Ames test, mouse lymphoma, or human lymphocyte tests, nor was it clastogenic *in vivo* in the mouse micronucleus test.

Pregnancy
Category C
Animal reproduction studies have not been conducted with MYOVIEW24. It is not known whether MYOVIEW24can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Therefore, MYOVIEW24 should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Technetium Tc99m pertechnetate can be excreted in human milk. Therefore, formula should be substituted for breast milk until the technetium has cleared from the body of the nursing woman.

Pediatric Use
Safety and effectiveness of MYOVIEW and MYOVIEW24 in pediatric patients have not been established. MYOVIEW24 is not for use in newborns (contains preservatives). (see WARNINGS)

ADVERSE REACTIONS

Adverse events were evaluated in clinical trials with MYOVIEW. These trials included 764 adults (511 men and 253 women) with a mean age of 58.7 years (range 29-94 years). The subjects received a mean dose of 7.67 mCi on the first injection and 22.4 mCi on the second injection of MYOVIEW.

Deaths did not occur during the clinical study period of 2 days. Six cardiac deaths occurred 3 days to 6 months after injection and were thought to be related to the underlying disease or cardiac surgery. After MYOVIEW injection, serious episodes of angina occurred in 3 patients.

Overall cardiac adverse events occurred in 5/764 (less than 1%) of patients after MYOVIEW injection.

The following events were noted in less than 1% of patients:
Cardiovascular: angina, hypertension, Torsades de Pointes
Gastrointestinal: vomiting, abdominal discomfort
Hypersensitivity: cutaneous allergy, hypotension, dyspnea
Special Senses: metallic taste, burning of the mouth, smelling something
There was a low incidence (less than 4%) of a transient and clinically insignificant rise in white blood cell counts following administration of the agent.

DOSAGE AND ADMINISTRATION

For exercise and rest imaging, MYOVIEW24 is administered in two doses:

The first dose of 5-8 mCi (185-296 MBq) is given at peak exercise.
The second dose of 15-24 mCi (555-888 MBq) is given approximately 4 hours later, at rest.

Imaging may begin 15 minutes following administration of the agent.

Dose adjustment has not been established in renally or liver impaired, pediatric or geriatric patients.

RADIATION DOSIMETRY

Based on human data, the absorbed radiation doses to an average human adult (70 kg) from intravenous injections of the agent under exercise and resting conditions are listed in Table 4. The values are listed in descending order as rad/mCi and μGy/MBq and assume urinary bladder emptying at 3.5 hours.

Table 4
Estimated Absorbed Radiation Dose (Technetium Tc99m Tetrofosmin Injection)

	Absorbed radiation dose			
	Exercise		Rest	
Target organ	rad/mCi	µGy/MBq	rad/mCi	µGy/MBq
Gall bladder wall	0.123	33.2	0.180	48.6
Upper large intestine	0.075	20.1	0.113	30.4
Bladder wall	0.058	15.6	0.071	19.3
Lower large intestine	0.057	15.3	0.082	22.2
Small intestine	0.045	12.1	0.063	17.0
Kidney	0.039	10.4	0.046	12.5
Salivary glands	0.030	8.04	0.043	11.6
Ovaries	0.029	7.88	0.035	9.55
Uterus	0.027	7.34	0.031	8.36
Bone surface	0.023	6.23	0.021	5.58
Pancreas	0.019	5.00	0.018	4.98
Stomach	0.017	4.60	0.017	4.63
Thyroid	0.016	4.34	0.022	5.83
Adrenals	0.016	4.32	0.015	4.11
Heart wall	0.015	4.14	0.015	3.93
Red marrow	0.015	4.14	0.015	3.97
Spleen	0.015	4.12	0.014	3.82
Muscle	0.013	3.52	0.012	3.32
Testes	0.013	3.41	0.011	3.05
Liver	0.012	3.22	0.015	4.15
Thymus	0.012	3.11	0.009	2.54
Brain	0.010	2.72	0.008	2.15
Lungs	0.008	2.27	0.008	2.08
Skin	0.008	2.22	0.007	1.91
Breasts	0.008	2.22	0.007	1.83

Dose calculations were performed using the standard MIRD method (MIRD Pamphlet No.1 (rev),Society of Nuclear Medicine, 1976). Effective dose equivalents (EDE) were calculated in accordance with ICRP 53 (Ann. ICRP 18 (1-4),1988) and gave values of 8.61×10^{-3} mSV/MBq and 1.12×10^{-2} mSV/MBq after exercise and rest, respectively.

INSTRUCTIONS FOR THE PREPARATION OF MYOVIEW24
USE ASEPTIC TECHNIQUE THROUGHOUT.

The user should wear waterproof gloves and use shielding at all times when handling the reconstituted vial or syringes containing the radioactive agent.

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

Preparation of Ascorbic Acid Injection, USP, Dilution in Bacteriostatic Sodium Chloride Injection, USP, 0.9%:

1) Place the sterile 0.45µm filter provided on the end of a sterile syringe and a needle on the end of the filter. Break the ampule of Ascorbic Acid Injection, USP and withdraw 0.7 mL through the filter into the syringe. (See PRECAUTIONS section of the Ascorbic Acid Injection, USP package insert.) The ampules should be stored in a refrigerator and should not be allowed to stand at room temperature before use. Failure to follow this caution may lead to excessive pressure inside the ampule. Wrap the container in a protective covering while it is being opened.
2) Remove and discard the filter and needle from the end of the syringe and replace them with a new, sterile needle. Transfer 0.5 mL of Ascorbic Acid Injection, USP into a 10 mL vial of Bacteriostatic Sodium Chloride Injection, USP, 0.9%. Gently invert the vial a few times to ensure thorough mixing.
3) Overlabel the 10 mL Bacteriostatic Sodium Chloride Injection, USP, 0.9% vial with the pre-printed label provided (24 mg/mL Ascorbic Acid Injection, USP, in Bacteriostatic Sodium Chloride Injection, USP, 0.9%). Use following dilution.

Labeling and Preparation of MYOVIEW24

1) Place one of the MYOVIEW vials in a suitable shielding container and sanitize the rubber septum.
2) Using a shielded, 10 mL sterile syringe, inject the required activity, as a volume of 1.5-5 mL up to 400 mCi/mL with a spcific activity of 14.8 GBq/mL, of technetium Tc99m generator eluate **(diluted with Sodium Chloride Injection, USP)** into the shielded vial (see Cautionary notes 1, 2 and 3 below). Before removing the syringe from the vial, withdraw an equivalent volume of gas from above the solution in order to equalize the pressure in the vial. Venting is not required.
3) Mix gently for 10 seconds to ensure complete dissolution of the powder.
4) Within 5 minutes add 0.2 mL of the 24 mg/mL Ascorbic Acid Injection, USP in Bacteriostatic Sodium Chloride Injection, USP 0.9% to the MYOVIEW vial. Gently invert the vial a few times to ensure thorough mixing.
5) Add the required volume of Bacteriostatic Sodium Chloride Injection, USP, 0.9% obtained from a 30 mL vial of Bacteriostatic Sodium Chloride Injection, USP, 0.9% (see Cautionary note 4).
6) Incubate at room temperature for 15 minutes.
7) Assay the total activity, complete the MYOVIEW24 user radiation label and attach it to the vial.
8) Visually inspect the reconstituted solution at a safe distance through leaded glass. Do not use if it is not clear or if it contains foreign particulate matter.
9) Maintain adequate shielding of the radioactive preparation.
10) Store the reconstituted injection at 2-25°C, 36-77°F and use within 24 hours of preparation.

Cautionary notes:

1) The volume of (diluted) technetium Tc99m generator eluate added to the vial must be in the range 1.5-5.0 mL.
2) The radioactive concentration of the (diluted) Tc99m generator eluate must not exceed 400 mCi/mL (14.8 GBq/mL) when it is added to the vial.
3) The generator eluate should be obtained from a generator with a previous elution of no more than 72 hours.
4) The volume of Bacteriostatic Sodium Chloride Injection, USP, 0.9% added to the preparation should be in the range 1.5-5.0 mL and must be equivalent to the volume of technetium Tc99m generator eluate added to the vial in Step 2 above.

5) The pH of the prepared injection should be in the range 6.7-8.2.
6) Safety and effectiveness of Technetium Tc99m Tetrofosmin Injection were established using investigational material shown to have a radiochemical purity of at least 90% prior to administration to patients in clinical studies.
7) The contents of the MYOVIEW vial are not radioactive. However, after the sodium pertechnetate Tc99m is added adequate shielding of the final preparation must be maintained.
8) The technetium Tc99m labeling reaction involved in the preparation of technetium Tc99m tetrofosmin injection depends on maintaining tin in the divalent (reduced) state. Any oxidant present in the sodium pertechnetate Tc99m used may adversely affect the quality of the preparation. Sodium pertechnetate Tc99m containing oxidants should not be used for the preparation of the labeled product.
9) The contents of the MYOVIEW vial are sterile and pyrogen-free. It is essential that the user follow the directions carefully, adhere to aseptic procedures during the preparation of the radiopharmaceutical, and review the PREPARATION, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS sections for Ascorbic Acid Injection, USP.
10) All dilutions of MYOVIEW24 preparations **MUST** be made using Bacteriostatic Sodium Chloride Injection, USP, 0.9% from the supplied 30 mL vial.

Quality Control

An assay of the radiochemical purity of the prepared injection can be performed using the following chromatographic procedure.

Equipment and eluent

1) Gelman ITLC/SG strip (2 cm x 20 cm)
2) Ascending chromatography tank and cover
3) 35:65 v/v mixture of acetone and dichloromethane
4) 1 mL syringe with 22-25 G needle
5) Suitable counting equipment

Method

1) Pour the 35:65 acetone:dichloromethane mixture into the chromatography tank to a depth of 1 cm. Cover the tank and allow to equilibrate with the solvent vapor.
2) Mark an ITLC/SG strip with a pencil line at 3 cm from the bottom and, using an ink marker pen, at 15 cm from the pencil line. The pencil line indicates the origin where the sample is to be applied and movement of color from the ink line will indicate the position of the solvent front when upward elution should be stopped.
3) Cutting positions at 3 cm and 12 cm above the origin (Rfs 0.2 and 0.8 respectively) should also be marked in pencil.
4) Using a 1 mL syringe and needle, apply a 10-20 µL sample of the prepared injection at the origin of the ITLC/SG. Place it in the chromatography tank immediately and replace the cover. Ensure that the strip is not adhering to the walls of the tank.
   Note: A 10-20 µL sample will produce a spot with a diameter of 7-10 mm. Smaller sample volumes have been shown to give unreliable radiochemical purity values.
5) When the solvent reaches the ink line, remove the strip from the tank and allow it to dry.

6) Cut the strip into 3 pieces at the marked cutting positions and measure the activity on each using suitable counting equipment. Try to ensure similar counting geometry for each piece and minimize equipment dead time losses.
7) Calculate the radiochemical purity from:

$$\% \text{ Technetium Tc99m Tetrofosmin} = \frac{\text{Activity of center piece}}{\text{Total activity of all 3 pieces}} \times 100$$

A value of at least 90% should be obtained in a satisfactory preparation.
Note: Free Tc99m pertechnetate runs to the top piece of the strip. Technetium Tc99m tetrofosmin runs to the center piece of the strip. Reduced hydrolyzed Tc99m and any hydrophilic complex impurities remain at the origin in the bottom piece of the strip.

HOW SUPPLIED

The kit contains:

(5) 10 mL vials	MYOVIEW containing a sterile, non-pyrogenic, freeze-dried mixture of tetrofosmin, stannous chloride dihydrate, disodium sulphosalicylate, sodium D-gluconate and sodium hydrogen carbonate.
(5) 1 mL ampuls	Ascorbic Acid Injection, USP
(5) 10 mL vials	Bacteriostatic Sodium Chloride Injection, USP, 0.9%
(5) 30 mL vials	Bacteriostatic Sodium Chloride Injection, USP, 0.9%
(1)	MYOVIEW24 Package Insert
(1)	Ascorbic Acid Injection, USP Package Insert
(5)	Pressure sensitive labels for 24 mg/mL Ascorbic Acid Injection, USP in Bacteriostatic Sodium Chloride Injection, USP, 0.9%
(5)	Pressure sensitive labels for MYOVIEW24 vials (reconstituted product)
(5)	Sterile 0.45µm filters

STORAGE
Store the kit in a refrigerator at 2-8°C (36-46°F).
The kit should be protected from light.

Store the reconstituted injection, for up to 24 hours at 2-25°C (36-77°F) using appropriate radiation shielding.

This reagent kit is approved for use by persons licensed by the Illinois Department of Nuclear Safety pursuant to 32 Ill. Code Adm. Section, Section 330.260(a) and 335.4010 or under equivalent licenses of the U.S. Nuclear Regulatory Commission, or an Agreement State.

MYOVIEW is manufactured by Nycomed Amersham, plc, United Kingdom
Bacteriostatic Sodium Chloride Injection, 0.9% USP is manufactured by American Pharmaceutical Partners, Los Angeles, CA, 90024
Ascorbic Acid Injection, USP is manufactured by Abbott Laboratories, Chicago, IL, 60064

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/s/

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