PRODUCT MONOGRAPH

MYOVIEW™
[Kit for the Preparation of Technetium Tc99m Tetrofosmin Injection]

Radiodiagnostic Agent

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NAME OF DRUG

MYOVIEW™ [Kit for the Preparation of Technetium Tc99m Tetrofosmin Injection]
Radiodiagnostic Agent
For intravenous use only

DESCRIPTION

Myoview is supplied as a package of five multidose vials for use in the preparation of a technetium Tc99m tetrofosmin intravenous injection to be used for scintigraphic imaging studies for the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium. Each vial contains a pre-dispensed, 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 17.4 µg), 0.32 mg disodium sulphosalicylate, 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. The product contains no antimicrobial preservative.

When sterile, pyrogen-free sodium pertechnetate Tc99m in isotonic saline is added to the vial, a Tc99m complex of tetrofosmin is formed. The pH of the reconstituted vial is 7.5-9.0.

Administration is by intravenous injection for diagnostic use.

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 - technetium Tc99m

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

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 0.2 mm. 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 2.7 mm 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 6.02 hours

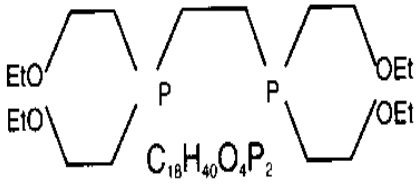
Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.399
2	0.795	9	0.355
3	0.708	10	0.317
4	0.631	11	0.282
5	0.563	12	0.252
6	0.502	24	0.063

*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.



The structural formula of tetrofosmin is:

Pharmacokinetics

Studies in normal volunteers have demonstrated rapid myocardial uptake of Tc99m tetrofosmin, and rapid blood, liver and lung clearances. Uptake in the myocardium is rapid reaching a maximum of about 1.2% of the injected dose (i.d.) at 5 minutes. Background activity is less than 5% i.d. after 10 minutes in the blood , less than 4.5% i.d. after 60 minutes in the liver and less than 2% i.d. after 30 minutes in the lung. 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

Studies in animals have shown that myocardial uptake of Tc99m tetrofosmin is linearly related to coronary blood flow, confirming the effectiveness of the complex as a myocardial perfusion imaging agent. Additional studies have been completed that conclude that Tc99m tetrofosmin is taken up/retained by the mitochondria of cardiac cells by a mechanism which is dependent on the mitochondrial membrane potential in a manner similar to that of other lipophilic technetium cationic complexes.

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 (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 infarcts 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 the two pivotal trials in which 83 subjects were administered dipyridamole stress, the sensitivity and specificity of Tc99m tetrofosmin SPECT imaging was studied in comparison to coronary angiography results. On a per subject basis, the sensitivity was 96% for both studies and the specificity was 31% for the one study that included 13 subjects without coronary artery disease, as confirmed by angiography. Overall image quality was evaluated in one pivotal trial; 86% of the subjects demonstrated quality evaluation scores of good or higher, and all had interpretable images.

Toxicology

Acute toxicity studies employing Myoview at dosage levels of approximately 1050 times the maximum human single dose failed to reveal mortality or any significant signs of toxicity in rats or rabbits. In repeated dose studies, some evidence of toxicity was observed in rabbits, but only at cumulative doses exceeding 10,000 times the maximum human single dose. In rats receiving these doses, there was no significant evidence of toxicity.

INDICATIONS AND CLINICAL USES

Myoview is indicated for scintigraphic imaging of the myocardium following separate administrations under stress (exercise and/or pharmacologic) and resting conditions in patients with known or suspected coronary artery disease. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium. Dipyridamole-induced pharmacologic stress may be used as an alternative to exercise in patients who cannot exercise adequately.

CONTRAINDICATIONS

None known.

WARNINGS

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.

Myoview is not recommended for use in patients with known hypersensitivity to tetrofosmin.

Severe hypersensitivity reactions and anaphylactoid reactions have been reported for Myoview.

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.

Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Caution should be used when dipyridamole-induced pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the Product Monograph and

instructions for dipyridamole (Persantine).

PRECAUTIONS

General

The contents of the kit are not radioactive. However, after the sodium pertechnetate Tc99m is added, adequate shielding of the final preparation must be maintained to minimize radiation exposure to occupational workers and patients.

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 Tc99m labeling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Therefore, sodium pertechnetate Tc99m containing oxidants should not be employed.

The components of the reagent vial are sterile and non-pyrogenic. It is essential that the user follows the directions carefully and adheres to strict aseptic technique.

Allergic reactions and anaphylaxis may occur with Myoview.

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 only by those practitioners who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

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 channel blockers and nitrates may influence myocardial function and blood flow. The effects of such drugs on imaging results are not known.

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.

Use in Pregnancy

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has adverse effects on the fetus, this radiopharmaceutical preparation should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards.

Nursing Mothers

Technetium Tc99m Pertechnetate can be excreted in human milk. Where an assessment of the risk to benefit ratio suggests the use of this product in lactating mothers, formula feeding should be substituted for breast feeding.

Pediatric Use

Adequate studies do not exist to support the use of this radiopharmaceutical in children.

ADVERSE REACTIONS

Adverse events were evaluated in clinical trials of 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 283.8 MBq (7.67 mCi) on the first injection and 828.8 MBq (22.4 mCi) on the second injection of Myoview.

Adverse events were also evaluated in clinical trials using pharmacologic or exercise stress. Four studies using a single pharmacologic stress agent were performed in 438 adults (232 men and 205 women; sex was not recorded for one subject) with a mean age of 65.4 years (range 27 - 97 years; age was not recorded for two subjects). In one of the studies the mean rest/first injection was 7.79 mCi and the mean stress/second dose was 33.79 mCi. In another study, the mean stress/first dose was 7.46 mCi and the mean rest/second dose was 22.12 mCi.

Adverse events were recorded in one multiple pharmacologic stress agent study of 49 adults (44 men and 5 women) with a mean age of 58.7 years (range 33.9 - 81.1 years). The study had stress, exercise and/or pharmacologic stress conditions. Under pharmacologic stress conditions the subjects received a mean dose of 29.01 - 29.34 mCi. Under rest conditions, the subjects received a mean dose of 28.03 mCi. Under exercise conditions, the subjects received a mean dose of 28.11 mCi.

There were no deaths in clinical trials within 2 days of Myoview administration. Cardiac deaths occurring 3 days to 6 months after injection were thought to be related to the underlying disease or cardiac surgery. After Myoview injection, serious episodes of angina occurred in four patients, and ventricular tachycardia in one patient

Overall cardiac adverse events occurred in 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, flushing
Gastrointestinal: vomiting, abdominal pain/discomfort
Hypersensitivity: cutaneous allergy, hypotension, dyspnea
Special Senses: metallic taste, burning of mouth, smelling something, abnormal vision

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.

Post-Market Adverse Drug Reactions
The following undesirable effects are recognised for MYOVIEW*:

SOC Immune system disorders

Hypersensitivity, anaphylactic or anaphylactoid shock, anaphylactic or anaphylactoid reaction

SOC Nervous system Disorders

Taste alteration, dizziness

SOC Cardiac Disorders

Tachycardia, chest pain

SOC Vascular disorders

Hypotension

SOC Respiratory, thoracic and mediastinal disorders

Dyspnoea, bronchospasm, throat tightness, coughing

SOC Gastrointestinal Disorders

Nausea, vomiting, abdominal pain

SOC Skin and Subcutaneous tissue Disorders

Urticaria, pruritus, rash, erythema, angioedema

* The list presented according to the MedDRA system organ classification.

DOSAGE AND ADMINISTRATION

For stress (either exercise- or dipyridamole-induced) and rest imaging, Myoview is administered in two doses:

The first dose of 185-300 MBq (5-8 mCi) is given at peak stress.

The second dose of 550-900 MBq (15-24 mCi) is given approximately 4 hours later, at rest.

SPECT 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. The patient doses should be measured using a suitably calibrated radioactivity dose calibrator immediately

prior to administration to the patient.

INSTRUCTIONS FOR PREPARATION AND USE

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.

1) Place one of the vials in a suitable shielding container and sanitize the rubber septum with the swab provided.

2) Insert a sterile 19G to 26G needle (the venting needle) through the rubber septum. Using a shielded, 10 mL sterile syringe, inject the required activity of up to 8.8 GBq (240 mCi) technetium Tc99m generator eluate (diluted with Sodium Chloride Injection USP) into the shielded vial (see Cautionary notes 1 and 2). Before removing the syringe from the vial, withdraw 2 mL of gas from above the solution. Remove the venting needle. Mix gently to ensure complete dissolution of the powder.

3) Incubate at room temperature for 15 minutes.

4) Assay the total activity, complete the user radiation label and attach it to the vial.

5) 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.

6) Maintain adequate shielding of the radioactive preparation.

7) Store the reconstituted product at 2-25^{o}C, 36-77^{o}F, and use within 12 hours of preparation.

8) The radiochemical purity of the reconstituted solution must be checked prior to administration to the patient.

Cautionary notes:

1) The volume of (diluted) technetium Tc-99m generator eluate added to the vial must be in the range of 4-8 mL.

2) The radioactive concentration of the (diluted) Tc99m generator eluate must not exceed

1.1 GBq/mL (30 mCi/mL) when it is added to the vial.

3) The pH of the prepared injection should be in the range of 7.5-9.0.

4) 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.

5) 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.

6) 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.

7) Sodium Chloride Injection USP must be used as the diluent. Do not use bacteriostatic sodium chloride as a diluent for sodium pertechnetate Tc99m injection because it may adversely affect the radiochemical purity and hence the biological distribution of the technetium Tc99m tetrofosmin injection.

8) The contents of the Myoview vial are sterile and pyrogen-free. The vial contains no bacteriostatic preservative. It is essential that the user follow the directions carefully and adhere to aseptic procedures during the preparation of the radiopharmaceutical.

Quality Control

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

Equipment and eluent

(1) GMCP SA[1] TLC strip (2cm x 20cm) – Do not heat activate
(2) Ascending chromatography tank and cover

(3) 65:35% v/v mixture of acetone and dichloromethane (prepared freshly)
(4) 1ml syringe with 22-25G needle
(5) Suitable counting equipment

[1]Glass Microfibre Chromatography Paper Impregnated with Silicic Acid

Method

(1) Pour the 65:35% v/v acetone:dichloromethane mixture into the chromatography tank to a depth of 1cm and cover the tank to allow the solvent vapour to equilibrate.
(2) Mark the TLC strip with a pencil line at 3cm from the bottom and, using an ink marker pen, at 15cm from the pencil line. The pencil line indicates the origin where the sample is to be applied and movement of colour from the ink line will indicate the position of the solvent front when upward elution should be stopped.
(3) Cutting positions at 3.75cm and 12cm above the origin (Rf's 0.25 and 0.8 respectively) should also be marked in pencil.
(4) Using a 1ml syringe and needle, apply a 10µl sample of the prepared injection at the origin of the strip. Do not allow the spot to dry. Place the strip in the chromatography tank immediately and replace the cover. Ensure that the strip is not adhering to the walls of the tank.

Note: A 10µl sample will produce a spot with a diameter of approximately 10mm. Different 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:

$$\% \text{ tetrofosmin } (^{99m}\text{Tc}) = \frac{\text{Activity of centre piece}}{\text{Total activity of all 3 pieces}} \times 100$$

Note: Free (^{99m}Tc) pertechnetate runs to the top piece of the strip. Tetrofosmin (^{99m}Tc) runs to the centre piece of the strip. Reduced hydrolysed-^{99m}Tc and any hydrophilic complex impurities remain at the origin in the bottom piece of the strip.

Do not use material if the radiochemical purity is less than 90%.

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
Gallbladder 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. [2] Effective dose equivalents (EDE) were calculated in accordance with ICRP 53 [3] and gave values of 31.9 mrem/mCi, 8.61 x 10^{-3} mSv/MBq and 41.4 mrem/mCi, 1.12 x 10^{-2} mSv/MBq after exercise and rest, respectively.

HOW SUPPLIED

The kit comprises five multidose vials, appropriate numbers of radiation labels, sanitizing alcohol swabs and a package insert. Each vial contains a sterile, non-pyrogenic, freeze-dried mixture of tetrofosmin, stannous chloride dihydrate, disodium sulphosalicylate, sodium D-gluconate and sodium hydrogen carbonate.

STORAGE

Store the kit in a refrigerator at 2-8°C, 36-46°F.
Store the reconstituted product at 2-25°C, 36-77°F, using appropriate radiation shielding.
The kit should be protected from light.

EXPIRY

Shelf-life of the Myoview kit, stored at 2-8°C, 36-46°F, is 52 weeks from the date of manufacture.
The reconstituted product should be used within 12 hours of preparation.

REFERENCES

(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.

(2) MIRD Pamphlet No. 1, Society of Nuclear Medicine, 1976.

(3) Ann. ICRP 18 (1-4), 1988.