Simplified Chromatographic Procedure for Rapid Quality Control (method 2):

Equipment and eluent

1. Solid Phase Extraction (SPE) C18 cartridge. (360mg Sorbent, 55 -105 µm particle size, e.g. Waters Sep-Pak® or equivalent)
2. 3 x 10ml vials and caps, Labelled "A", "B" and C
3. Lead pots
4. 0.9% Sodium chloride
5. Ethanol
6. Dose calibrator

Method

Note: all loading steps (sample and solvents) must be performed using a slow flow rate (i.e. drop by drop application of the mobile phase). If the flow is too high, components may not interact sufficiently with the stationary phase which will give an inaccurate result for radiochemical purity.

1. Place the cartridge in the correct orientation (short end facing upwards) in a clamp stand and place behind a suitable lead shield
2. Place the vial labelled 'A' under the cartridge as a collection vial.
3. Condition the stationary phase by flushing with 2ml 0.9% Sodium Chloride collecting in vial 'A'.
4. Carefully load 25 - 50µL of the preparation onto the cartridge.
5. Elute the cartridge with 2ml 0.9% Sodium chloride, collecting the eluate in vial 'A'.
6. Cap vial 'A' and place in a shielded container. Cap and retain for measurement.
7. Place vial 'B' under the cartridge as a collection vial.
8. Elute the cartridge with 5ml ethanol, collecting the eluate in vial 'B'.
9. Cap vial 'B' and place in a shielded container. Cap and retain for measurement.
10. Remove the SPE cartridge using tweezers and place into vial 'C' and place in a shielded container. Cap and retain for measurement.
11. Measure the activity of each of the vials labelled A to C using a dose calibrator. Under the test conditions employed:

    Free ^{99m}Tc O4- (pertechnetate) is eluted from the cartridge with 2ml 0.9% Sodium Chloride (Vial A)

    99mTc - tetrofosmin is retained on the stationary phase and is eluted with 5ml ethanol (Vial B)

    Reduced hydrolysed ^{99m}Tc (RHT) and hydrophilic impurities remain on the cartridge (Vial C)

12. Calculate the % ^{99m}Tc-tetrofosmin as follows:

$$\%\ \text{RCP}\ (^{99m}\text{Tc-tetrofosmin}) = \frac{\text{Activity in vial B}}{\text{Sum of activity in vial A + B + C}} \times 100$$

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

Overdose

In cases of overdosage of radioactivity frequent micturition and defaecation should be encouraged in order to minimize radiation dosage to the patient.

Side-effects

Adverse reactions following administration of ^{99m}Tc Tetrofosmin are very rare (0.01%). A few patients have experienced a feeling of bodily warmth, vomiting (12-24 hours post-injection), headache, dizziness, a transient metallic taste, disturbance of smell or a mild burning sensation in the mouth after injection. In addition, hypersensitivity reactions have occurred including flushing, itching, urticarial or erythematous rash, facial oedema, hypotension and dyspnoea. Some reactions were delayed by several hours following administration of ^{99m}Tc-tetrofosmin. Transient rises in white blood cell counts have also been reported in a small number of patients. Isolated cases of serious reactions have been reported, including anaphylactic reaction (0.001%) and severe allergic reaction (single report).

In case of side-effects following administration of radiopharmaceuticals, users should ensure the availability of appropriate medical treatment at the time of administration of any radiopharmaceutical to the patient. Users are requested to report to GE Healthcare Limited any instances of suspected adverse drug reactions or side-effects associated with the use of this product.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic result. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse events will occur with negligible frequency because of the low radiation dose incurred.

For most diagnostic investigations using a nuclear medicine procedure the radiation dose (ED or using the previous nomenclature, EDE) delivered is less than 20mSv. Higher doses may be justified in some clinical circumstances.

Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceutical for cardiovascular system imaging, ATC Code : V09G A 02.

Pharmacological effects are not expected following intravenous administration of reconstituted Myoview at the recommended dosage. Studies in animals have shown that myocardial uptake of ^{99m}Tc-tetrofosmin is linearly related to coronary blood flow, confirming the effectiveness of the complex as a myocardial perfusion imaging agent.

Limited data in animals show uptake of ^{99m}Tc-tetrofosmin into breast tumour cells.

Pharmacokinetic properties

^{99m}Tc-tetrofosmin is rapidly cleared from the blood after intravenous injection; less than 5% of the administered activity remains in whole blood at 10 minutes post-injection. Background tissue clearance is rapid from lung and liver and activity is reduced in these organs following exercise, with enhanced sequestration in skeletal muscle. Approximately 66% of the injected activity is excreted within 48 hours post-injection, with approximately 40% excreted in the urine and 26% in the faeces.

Myocardial Uptake:

Uptake in the myocardium is rapid, reaching a maximum of about 1.2% of injected dose with sufficient retention to allow imaging of the myocardium by planar or SPECT techniques from 15 minutes up to 4 hours post-administration.

Preclinical safety data

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. Studies on reproductive toxicity have not been conducted. Tetrofosmin showed no evidence of mutagenic potential in *in vitro* or *in vivo* mutagenicity studies. Studies to assess the carcinogenic potential of Myoview have not been performed.

Radiation dosimetry

Estimated absorbed radiation doses for an average adult patient (70kg) from intravenous injections of 99mTc-tetrofosmin are listed below. The values are calculated assuming urinary bladder emptying at 3.5 hour intervals. Frequent bladder emptying should be encouraged after dosing to minimise radiation exposure.

The table below shows the dosimetry according to ICRP Publication 128 (International Commission of Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances, Ann ICRP 2015).

	Absorbed dose per unit of activity administered (mGy/MBq)	
Organ	**Exercise**	**Rest**
Adrenals	4.40E-03	4.20E-03
Bone surfaces Brain Breast	6.3E-03 2.7E-03 2.3E-03	5.8E-03 2.3E-03 2.0E-03
Gallbladder wall Gastrointestinal tract Stomach wall Small intestine wall Colon wall (Upper large intestine wall) (Lower large intestine wall)	2.7E-02 4.6E-03 1.1E-02 1.8E-02 2.0E-02 1.5E-02	3.6E-02 4.5E-03 1.5E-02 2.4E-02 2.7E-02 2.0E-02
Heart wall	5.2E-03	4.7E-03
Kidneys	1.0E-02	1.3E-02
Liver	3.3E-03	4.0E-03
Lungs	3.2E-03	2.8E-03
Muscles	3.5E-03	3.3E-03
Oesophagus	3.3E-03	2.8E-03
Ovaries	7.7E-03	8.8E-03
Pancreas	5.0E-03	4.9E-03
Red marrow	3.9E-03	3.8E-03
Skin	2.2E-03	2.0E-03
Spleen	4.1E-03	3.9E-03
Testes	3.4E-03	3.1E-03
Thymus	3.3E-03	2.8E-03
Thyroid	4.7E-03	5.5E-03
Urinary bladder wall	1.4E-02	1.7E-02
Uterus	7.0E-03	7.8E-03
Remaining organs	3.8E-03	3.8E-03
Effective Dose (mSv/MBq)	**6.9E-03**	**8.0E-03**

The effective dose (ED) resulting from the administration of doses of reconstituted Myoview of 250MBq after exercise and 750MBq at rest is 1.73mSv after exercise and 6.00mSv at rest (per 70kg individual). If doses are calculated on the basis of the previously used effective dose equivalent (EDE), values are 2.15mSv and 8.38mSv respectively.

Nuclear data for technetium-99m

Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. is produced by a [^{99}Mo/^{99m}Tc] generator. Technetium-99m disintegrates with the emission of gamma radiation (energy 141keV, 88.5%; 143keV, 0.03%) and a half life of 6.02 hours).
The dose rate at 0.5m from a vial containing 1.11GBq Technetium-99m will be reduced to less than 2.5µSv/h by shielding with 2mm lead.

Expiry

The product must not be used after the expiry date which is stated on the packaging.

Storage

Store at 2-8°C in the original package. Chemical and physical in-use stability of the reconstituted solution for injection has been demonstrated for 12 hours at 2°C-25°C. Store the reconstituted product below 25°C. Do not freeze.

Date of preparation

August 2020

Product Registration:

SIN 11820P

European patent EP 311352B
European patent application No: 89303374.6

GE Healthcare AS
Oslo, Norway

GE Healthcare

TECHNICAL LEAFLET

MYOVIEW™

(Kit for the preparation of ^{99m}Tc-tetrofosmin)

1199210

1199210 SGP

Presentation
Each vial contains 230 micrograms tetrofosmin (active ingredient), 0.03mg stannous chloride dihydrate, 0.32mg disodium sulphosalicylate, 1.0mg sodium D-gluconate and 1.8mg sodium hydrogen carbonate as a freeze-dried mixture sealed under nitrogen.

Radiopharmaceutical kit - powder for solution for injection following reconstitution with 4-8ml of sterile Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. at a radioactive concentration not exceeding 1.5GBq/ml to yield ^{99m}Tc-tetrofosmin injection, a diagnostic radiopharmaceutical imaging agent.
The product is supplied in a 10ml clear glass vial. Packs of 2 and 5 vials are available. Labels for the reconstituted product and sanitizing swabs (containing 70% isopropyl alcohol B.P.) are provided.

The reconstituted injection contains 3.6 - 3.7 mg/ml sodium.

Product Registrant
GE Healthcare Pte Ltd
11 North Buona Vista Drive
#11-07 The Metropolis
Singapore 138589

Manufacturer
GE Healthcare AS
Nycoveien 1
NO-0485 Oslo
Norway

Indications
This medicinal product is for diagnostic use only.
Myocardial Imaging:
Myoview is a myocardial perfusion agent indicated as an adjunct in the diagnosis and localization of myocardial ischaemia and/or infarction.

Breast Tumour Imaging:
Myoview is indicated as an adjunct to the initial assessments (e.g palpation, mammography, or alternative imaging modalities and/or cytology) in the characterisation of malignancy of suspected breast lesions where all these other recommended tests were inconclusive.

Contra-indications
Myoview is contraindicated in pregnancy and in patients with known hypersensitivity to tetrofosmin or any of the excipients.

Precautions for use
Breast lesions less than 1cm in diameter may not all be detected with scintimammography as the sensitivity of Myoview for the detection of these lesions is 36% (n=5 of 14, 95% CI 13% to 65%) relative to histological diagnosis. A negative examination does not exclude breast cancer especially in such a small lesion. Efficacy in the identification of auxiliary lesions has not been proven, consequently scintimammography is not indicated for staging breast cancer.

This product is not to be administered directly to the patient. The contents of the vial are intended only for use in the preparation of a radioactive technetium-99m labelled injection, using the procedures described in this pack leaflet.

Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides. They may be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

The normal precautions for handling radioactive materials should also be observed. For details of the storage, elution, handling and disposal of the ^{99m}Tc sterile generator used as the source of Sodium Pertechnetate [^{99m}Tc] Injection required for reconstitution of MYOVIEW™ the user is referred to the instructions for use supplied with the generator by the manufacturer.

Interactions
The interaction of Myoview with other drugs has not been systematically investigated, however no interactions were reported in clinical studies in which Myoview was administered to patients receiving comedication. Drugs which influence myocardial function and/or blood flow, for example, beta blockers, calcium antagonists or nitrates, can lead to false negative results in diagnosis of coronary artery disease. The results of imaging studies should always, therefore, be considered in the light of current medication.

Warnings
This medicinal product contains 3.6 - 3.7 mg/ml sodium. This needs to be taken into consideration for patients on a controlled sodium diet.

As part of the manufacture, the vial of freeze-dried product is filled with an inert nitrogen atmosphere to a pressure just below atmospheric before being sealed with the rubber closure. The product does not contain an antimicrobial preservative. ^{99m}Tc-tetrofosmin should not be mixed or diluted with any substance other than those recommended for reconstitution.

This product is a component for use in the preparation of a radioactive injection intended for pharmaceutical use. Because of the small mass of chemical substances present, there is negligible risk to persons handling or administering the material, other than that from the radioactive nature of the reconstituted product.

Pregnancy and Lactation
Myoview is contraindicated in pregnancy. Animal reproductive toxicity studies have not been performed with this product. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Administration of ^{99m}Tc-tetrofosmin at doses of 250MBq at exercise, followed by 750MBq at rest results in an absorbed dose to the uterus of 7.6mGy. A radiation dose above 0.5mGy (equivalent to the exposure from annual background radiation) would be regarded as a potential risk to the foetus.

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. It is not known whether ^{99m}Tc-tetrofosmin is secreted in human milk, therefore if administration is considered necessary, formula feeding should be substituted for breast feeding for at least 12 hours.

Dosage and administration
Paediatric Population
Myoview is not recommended for use in children or adolescents as data are not available for these age groups.

Adults
Myocardial Imaging
Patients should be requested to fast overnight or to have only a light breakfast on the morning of the procedure.

For the diagnosis and localization of myocardial ischaemia the recommended procedure involves two intravenous injections of ^{99m}Tc-tetrofosmin. For adults and the elderly 185-250MBq is given at peak exercise, followed by 500-750MBq given at rest approximately 4 hours later. The activity administered should be restricted to 1000MBq in any one day.

As an adjunct in the diagnosis and localization of myocardial infarction, one injection of ^{99m}Tc-tetrofosmin (185-250MBq) at rest is sufficient.

Planar or preferably SPECT imaging should begin no earlier than 15 minutes post-injection. There is no evidence for significant changes in myocardial concentration or redistribution of ^{99m}Tc-tetrofosmin, therefore, images may be acquired up to at least four hours post-injection. For planar imaging the standard views (anterior, LAO 40°-45°, LAO 65°-70° and/or left lateral) should be acquired.

Breast Imaging
For the diagnosis and localization of suspected breast lesions, the recommended procedure involves a single intravenous injection of ^{99m}Tc-tetrofosmin between 500–750MBq. The injection should preferably be given in a foot vein or a site other than the arm on the side of the suspected breast lesion. The patient does not need to fast before the injection.

Breast imaging is optimally initiated 5–10 minutes post-injection with the patient in the prone position with the breast(s) freely pendant. A special imaging couch designed for nuclear medicine breast imaging is recommended. A lateral image of the breast suspected of containing the lesions should be obtained with the camera face as close to the breast as is practicable.

The patient should then be repositioned so that a lateral image of the pendant contralateral breast can be obtained. An anterior supine image may then be obtained with the patient's arms behind her head.

Procedure for the preparation of ^{99m}Tc-tetrofosmin
Normal safety precautions for the handling of radioactive materials should be observed in addition to the use of aseptic technique to maintain sterility of the vial contents.

Procedure for the preparation of ^{99m}Tc-tetrofosmin:
Use aseptic technique throughout.

1. Place the vial in a suitable shielding container and sanitize the rubber septum with the swab provided.
2. Insert a sterile needle (the venting needle, see Note 1) through the rubber septum. Using a shielded, 10ml sterile syringe, inject the required activity of Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. (appropriately diluted with 0.9% Sodium Chloride Injection BP) into the shielded vial (see Notes 2 to 4). Before removing the syringe from the vial, withdraw 5ml of gas from above the solution (see Note 5). Remove the venting needle. Shake the vial to ensure complete dissolution of the powder.
3. Incubate at room temperature for 15 minutes.
4. During this time assay the total activity, complete the user label provided and attach it to the vial.
5. Store the reconstituted injection at 2-25°C and use within 12 hours of preparation. Dispose of any unused material and its container via an authorised route.

Notes:
1. A needle of size 19G to 26G may be used.
2. The Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. used for reconstitution should contain less than 5ppm aluminium.
3. The volume of diluted Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. added to the vial must be in the range 4-8ml.
4. The radioactive concentration of the diluted Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. must not exceed 1.5GBq/ml when it is added to the vial.
5. For preparation volumes of more than 6ml, the remaining vial headspace is less than the 5ml added air volume. In these cases, the withdrawal of a 5ml volume of gas ensures that all of the vial headspace is replaced by air.
6. The pH of the prepared injection is in the range 7.5-9.0.
7. Studies have demonstrated that satisfactory radiochemical purity is achieved when Myoview is reconstituted with Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. eluted up to 6 hours previously from a generator last eluted within 72 hours.

Radiochemical purity measurement
Radiochemical purity may be checked using the following procedures:
Radiochemical Purity (RCP) by ascending chromatography on TLC-SA (method 1).

Equipment and eluent
1. Glass Microfiber Chromatography Paper impregnated with Silicic Acid (GMCP-SA) TLC strip (2cm x 20cm) - Do not heat activate.
2. Ascending chromatography tank and cover
3. 65:35% v/v acetone: dichloromethane mixture (prepared fresh daily)
4. 1ml syringe with 22-25G needle
5. Suitable counting equipment

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 a Glass Microfiber Chromatography Paper impregnated with Silicic Acid (GMCP-SA) 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 10 µl sample of the prepared injection at the origin of the strip. Do not allow the applied sample to come into contact with the pencil mark. 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 10 µl 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:

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

Note: Free [^{99m}Tc] pertechnetate runs to the top piece of the strip. ^{99m}Tc-tetrofosmin 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%.