Myoview™

1 NAME OF THE MEDICINAL PRODUCT

MYOVIEW 230 micrograms kit for radiopharmaceutical preparation.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 230 micrograms of tetrofosmin.

Excipients with known effect:

The reconstituted injection contains 0.08-0.16mg/ml sodium

For the full list of excipients, see section 6.1.

Myoview is reconstituted with Sodium Pertechnetate (^{99m}Tc) Injection Ph.Eur. (not included in this kit) to prepare technetium (^{99m}Tc) tetrofosmin injection.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

A white powdery solid.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 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.

4.2 Posology and method of administration

Posology

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 diagnosis and localization of myocardial ischaemia (using planar or SPECT techniques), the usual procedure involves two intravenous injections of tetrofosmin (^{99m} Tc), one given at peak stress and one given at rest. The order of the two administrations can be either rest first and stress second or stress first and rest second.

When rest and stress injections are administered on the same day, the activity administered for the second dose should result in a myocardial count rate at least three times greater than that of the residual activity from the first dose. The recommended activity range for the first dose is 250-400 MBq; the recommended activity range for the second dose given at least 1 hour later, is 600-800 MBq.

When rest and stress injections are administered on different days, the recommended activity range for each dose of tetrofosmin (^{99m} Tc) is 400-600 MBq. For studies on larger individuals (e.g. those with abdominal obesity or women with large breasts), use of activities at the higher end of this range is warranted.

The total activity administered for stress and rest myocardial imaging studies, whether performed on one or two days, should be restricted to 1200 MBq.

As an adjunct in the diagnosis and localization of myocardial infarction, one injection of tetrofosmin (^{99m} Tc) (250-400 MBq) 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 tetrofosmin (^{99m} Tc), therefore, images may be acquired up to at least four hours post injection.

For planar imaging the standard views (anterior, LAO 40º-45º, LAO 65º-70º 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 tetrofosmin (^{99m} Tc) between 500– 750 MBq. 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 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 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.

<u>Method of administration</u>
This medicinal product should be reconstituted before administration to the patient.
For instructions on reconstitution of the medicinal product before administration, see section 8.
For patient preparation, see section 4.4

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Must not be given during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
The possibility of hypersensitivity including anaphylactic/anaphylactoid reactions should always be considered. Advanced life support facilities should be readily available.

Paediatric population
Paediatric population, see section 4.2.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Renal impairment and hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation.

Breast lesions less than 1 cm 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 axillary lesions has not been proven; consequently scintimammography is not indicated for staging breast cancer.

In myocardial scintigraphy investigations under stress conditions, the contraindications associated with the induction of stress should be considered.

Precautions with respect to environmental hazard see section 6.6

Specific warnings
This medicinal product contains 0.08-0.16mg/ml sodium. This needs to be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No formal studies on the interaction of Myoview with other drugs have been performed. 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, e.g. 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
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.

Pregnancy
Myoview is contraindicated in pregnancy (see section 4.3). 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 250 MBq tetrofosmin (^{99m}Tc) at exercise, followed by 750 MBq at rest results in an absorbed dose to the uterus of 8.1 mGy. A radiation dose above 0.5 mGy (equivalent to the exposure from annual background radiation) would be regarded as a potential risk to the foetus.

Breast feeding
Before administering a radiopharmaceutical to a mother who is breast feeding consideration should be given to the possibility of delaying the administration of a radionuclide until the mother has ceased breast feeding and to what is the most appropriate choice of radiopharmaceutical, bearing in mind the secretion of activity in breast milk. It is not known whether tetrofosmin (^{99m}Tc) is secreted in human milk, therefore if administration is considered necessary, formula feeding should be substituted for breast feeding for at least 12 hours.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The frequencies of the undesirable effects are defined as follows:
Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very Rare (<1/10,000) and not known (cannot be determined with the data available).
Adverse drug reactions following administration of tetrofosmin (^{99m}Tc) are very rare (less than 1 in 10,000).

The following undesirable effects are recognised for Myoview:

Immune system disorders
Face oedema, hypersensitivity reaction, allergic reaction, anaphylactic reaction

Nervous system disorders
Headache, dizziness, taste metallic, disturbances of smell and taste

Vascular disorders
Flushing, hypotension

Respiratory, thoracic and mediastinal disorders
Dyspnoea

Gastrointestinal disorders
Vomiting, nausea, burning mouth

Skin and subcutaneous tissue disorder
Urticaria, itching, erythematous rash

General disorders and administration site condition
Feeling of warmth

Investigations
White blood cell count increased

Some reactions were delayed by several hours following administration of tetrofosmin (^{99m}Tc). Isolated cases of serious reactions have been reported, including anaphylactic reaction (less than 1 in 100,000) and severe allergic reaction (single report).

Since the administered substance quantity is very low, the major risk is caused by the radiation. Exposure to ionising radiation is linked with cancer induction and a potential for developing hereditary defects.

As the effective dose is 8.5 mSv when the maximal recommended activity of 1200 MBq is administered these adverse reactions are expected to occur with a low probability.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, cardiovascular system, technetium (^{99m}Tc) tetrofosmin, ATC Code: V09GA02.

Pharmacological effects are not expected following intravenous administration of reconstituted Myoview at the recommended dosage. Studies in animals have shown that myocardial uptake of tetrofosmin (^{99m}Tc) 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 tetrofosmin (^{99m}Tc) into breast tumour cells.

5.2 Pharmacokinetic properties

Organ uptake
Myocardial 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.

Elimination
Tetrofosmin (^{99m}Tc) 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.

Half-life
Sodium Pertechnetate (^{99m}Tc) Injection Ph.Eur. is produced by a [^{99}Mo/^{99m}Tc] generator. Technetium (^{99m}Tc) disintegrates with the emission of gamma radiation (energy 141 keV) and a half-life of 6.02 hours.

Renal/hepatic impairment
The pharmacokinetics in patients with renal or hepatic impairment has not been characterized.

5.3 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 vitro* or *in vivo* mutagenicity studies. Studies to assess the carcinogenic potential of Myoview have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Sodium D-gluconate
Disodium sulphosalicylate
Stannous chloride dihydrate
Nitrogen gas

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 8.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Chemical and physical in-use stability of the reconstituted solution for injection has been demonstrated for 12 hours at 2°C-8°C.

Store the reconstituted product in a refrigerator (2°C-8°C).

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Store in the original package in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

Storage should be in accordance with national regulations for radioactive materials.

6.5 Nature and contents of container

The product is supplied in a 10 ml clear glass vial sealed with a chlorobutyl rubber closure and flip off overseal.

Pack sizes: 2 or 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The reconstituted product is a clear colourless solution.

General warning
Radiopharmaceuticals should 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 licences of the competent official organisations.
Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.
Contents of the vial are intended only for use in the preparation of technetium (^{99m}Tc) tetrofosmin injection and are not to be administered directly to the patient without first undergoing the preparative procedure.
For instructions on reconstitution of the medicinal product before administration, see section 8.
If at any time in the preparation of this product the integrity of this vial is compromised it should not be used.
Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.
The content of the kit before reconstitution is not radioactive. However, after sodium pertechnetate (^{99m}Tc), Ph. Eur. is added, adequate shielding of the final preparation must be maintained.
The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of as radioactive waste via authorised route.

7. DOSIMETRY

Technetium (^{99m}Tc) is produced by means of a (^{99}Mo/^{99m}Tc) generator and decays with the

emission of gamma radiation with a mean energy of 140keV and a half-life of 6.02 hours to technetium (^{99}Tc) which, in view of its long half-life of 2.13 x 10^5 years can be regarded as quasi stable.

The estimated absorbed radiation doses to an average adult patient (70kg) from intravenous injections of tetrofosmin (^{99m}Tc) 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 minimize radiation exposure.

	Absorbed dose per unit of activity administered (mGy/MBq)	
Organ	**Exercise**	**Rest**
Heart Wall	4.1E-03	4.0E-03
Breasts	2.2E-03	1.8E-03
Gallbladder wall	3.3E-02	4.9E-02
Upper large intestine	2.0E-02	3.0E-02
Lower large intestine	1.5E-02	2.2E-02
Urinary bladder wall	1.6E-02	1.9E-02
Small intestine	1.2E-02	1.7E-02
Kidney	1.0E-02	1.3E-02
Salivary glands	8.0E-03	1.2E-02
Ovaries	7.9E-03	9.6E-03
Uterus	7.3E-03	8.4E-03
Bone surface	6.2E-03	5.6E-03
Thyroid	4.3E-03	5.8E-03
Pancreas	5.0E-03	5.0E-03
Stomach	4.6E-03	4.6E-03
Adrenals	4.3E-03	4.1E-03
Red Marrow	4.1E-03	4.0E-03
Spleen	4.1E-03	3.8E-03
Muscle	3.5E-03	3.3E-03
Testes	3.4E-03	3.1E-03
Liver	3.2E-03	4.2E-03
Thymus	3.1E-03	2.5E-03
Brain	2.7E-03	2.2E-03
Lungs	2.3E-03	2.1E-03
Skin	2.2E-03	1.9E-03
Effective Dose (mSv/MBq)	**6.0 E-03**	**7.2 E-03**

^{99m}Tc-tetrofosmin is administered as two intravenous injections either rest first and stress second or stress first and rest second. The recommended activity range for the first dose is 250-400 MBq; the recommended activity range for the second dose given at least 1 hour later, is 600-800 MBq.

The effective dose after administration of 800 MBq at rest or in breast imaging is 5.7 mSv (per 70 kg adult patient).

The absorbed radiation dose for the resting subject in the heart is 4.0E-03 mGy/MBq and after exercise is 4.1E-03 mGy/MBq. In the breast the absorbed radiation dose in breast imaging is 1.8E-03 mGy/MBq. The absorbed radiation dose in the bladder (3.5 hour voiding) is 1.6E-02 mGy/MBq after exercise and is 1.9E-02 mGy/MBq at rest or in breast imaging.

8. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

If the integrity of this vial is compromised, the product should not be used.

Method of preparation:
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 a) through the rubber septum. Using a shielded, 10 ml 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 b to d). Before removing the syringe from the vial, withdraw 5 ml of gas from above the solution (see Note e). 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 2-8°C and use within 12 hours of preparation. Dispose of any unused material and its container via an authorised route.

Notes:

(a) A needle of size 19G to 26G may be used.
(b) The Sodium Pertechnetate (^{99m}Tc) Injection Ph.Eur. used for reconstitution should contain less than 5ppm aluminium.
(c) The volume of diluted Sodium Pertechnetate (^{99m}Tc) Injection Ph.Eur. added to the vial must be in the range 4-8 ml.
(d) The radioactive concentration of the diluted Sodium Pertechnetate (^{99m}Tc) Injection Ph.Eur. must not exceed 1.5 GBq/ml when it is added to the vial.
(e) For preparation volumes of more than 6 ml, the remaining vial headspace is less than the 5 ml added air volume. In these cases, the withdrawal of a 5 ml volume of gas ensures that all of the vial headspace is replaced by air.
(f) The pH of the prepared injection is in the range 7.5-9.0.

Quality Control:

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 10µl 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 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:-

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

Note: Free (^{99m}Tc) pertechnetate runs to the top piece of the strip. 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%.

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

Equipment and eluent

(1) Solid Phase Extraction (SPE) C18 cartridge (360 mg 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 $^{99m}Tc\ O_4^-$ (pertechnetate) is eluted from the cartridge with 2ml 0.9% Sodium Chloride (Vial A)
- ^{99m}Tc - 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 % 99mTc-tetrofosmin as follows:

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

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

9. MANUFACTURERS

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11. REGISTRATION NUMBER

100-19-28394

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