SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PoltechMIBI, 1 mg, kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains
Active substance
[Tetrakis(2-methoxy-2-methylpropyl-1-isocyanide) copper(1+)]tetrafluoroborate 1.00 mg

The radionuclide is not part of the kit.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only. For intravenous injection after radiolabelling with sodium (Tc-99m) pertechnetate solution. PoltechMIBI using scintigraphy is indicated for:
- diagnosis of ischaemic heart disease.
- diagnosis and localisation of myocardial infarction.
- assessment of global ventricular function (first pass technique for determination of ejection fraction and/or regional wall motion).
- diagnosis of malignancy in patients who are suspected of cancer in the breast combined with inconclusive mammography or palpable tumour and negative or inconclusive mammography.
- diagnosis of patients with recurrent or persistent hyperparathyroidism.

4.2 Posology and method of administration

This medicinal product is administered intravenously and should be reconstituted before administration to the patient. The vial is reconstituted with a maximum of 11 GBq of oxidant-free sodium (Tc-99m) pertechnetate solution for injection in 1 - 5 ml.
Not less than 5 ml will be used for the highest activity of 11 GBq. Radiochemical purity should be checked prior to patient administration. For instruction on reconstitution of the medicinal product before administration, see section 12.
For patient preparation, see section 4.4.

The suggested dose range for intravenous administration to a patient of average weight (70 kg) is:

Diagnosis of ischaemic heart disease
Two injections are required (at stress and at rest) in order to differentiate between transient and persistent perfusion defects.
For the two-day stress/rest protocol 600 – 900 MBq per study.
For the one-day protocol 400 – 500 MBq for the first injection and 2.5 - 3 times more for the second injection.

The one-day protocol may be performed in either order (stress/rest or rest/stress) but the two injections should be administered at least two hours apart. This time interval, however, depends on the dose administered and is based on physical decay of Tc-99m. After the stress injection, exercise should be encouraged for an additional one minute (if possible).

Diagnosis of myocardial infarction
400 - 900 MBq
For diagnosis of myocardial infarction one injection at rest may be sufficient.

Assessment of global ventricular function and/or regional wall motion
600 - 800 MBq
Injected as a bolus.

For breast imaging
740 - 1100 MBq
Injected as a bolus.

For parathyroid imaging
185 - 925 MBq (the typical activity is 740 MBq)
Injected as a bolus.
(The dose used should in every case be as low as reasonably practical).

In light of the European Directive 97/43/Euratom and current practice throughout Europe, the above activities for Tc-99m sestamibi should be considered only as a general indication. It should be noted that in each country nuclear medicine physicians should respect the diagnostic reference levels (DRL) and the rules laid down by the local legislation. The injection of activities greater than local DRLs should be justified.

Cardiac imaging
If possible, patients should fast for at least four hours prior to the study. It is recommended that patients eat a light fatty meal or drink a glass or two of milk after each injection, prior to imaging. This will promote rapid hepatobiliary clearance of technetium Tc-99m sestamibi resulting in less liver activity in the image.

The heart to background ratio will increase with time but the ideal imaging time, reflecting the best compromise between heart count rate and contrast, is approximately 15 - 60 min. after a stress injection and 30 - 60 min. after a rest injection. Longer delays are required for resting images and for stress with vasodilators alone because of the risk of higher subdiaphragmatic Tc-99m activity. There is no evidence for significant changes in myocardial tracer concentration or redistribution, therefore imaging for up to 6 hours post injection is possible.

Either planar or tomographic imaging can be performed for diagnosis of ischemic heart disease and myocardial infarction, although SPECT (single photon emission computed tomography) should be performed whenever possible. Both may be ECG gated.

For planar imaging the standard three view (anterior, LAO 45º, LAO 70º or LL) planar projections should be used (e.g. 5 - 10 minutes each).

For tomographic imaging each projection should be acquired for approximately 20 - 40 seconds depending on injected dose.

For assessment of **global ventricular function** the same standard techniques and projections can be used, as established for Tc-99m first pass ejection studies; data should be acquired in list or fast frame mode in a computer using a high count rate scintillation camera. Gated Blood Pool Imaging protocols may be used for assessment of regional wall motion, however, must only be evaluated visually.

Breast imaging
The product is administered in the arm vein contralateral to the breast with the suspected lesion. If bilateral lesions are suspected, or if the patient has had previous mastectomy, the injection is ideally administered in a dorsal vein of the foot.

Breast imaging is optimally initiated 5 to 10 minutes post injection with the patient in the prone position with breast freely pendant. A 10 minutes lateral images of the breast suspected of containing cancer should be obtained with the camera face as close to the breast as practical.
The patient should then be repositioned so that the contralateral breast is pendant and a lateral image of it should be obtained. An anterior supine image may then be obtained with the patient's arms behind her head.

Parathyroid imaging
For the subtraction technique, either iodine (I-123) or Tc-99m pertechnetate can be used, followed by Tc-99m sestamibi, or Tc-99m sestamibi can be given first, followed by Tc-99m pertechnetate (I-123 can not be administered after Tc-99m sestamibi).
When I-123 is used, 7.5 to 20 MBq of oral iodine (I-123) are administered. Four hours after the administration of I-123, neck and thorax images are obtained. After I-123 image acquisition, 185 to 740 MBq of Tc-99m sestamibi are injected and images acquired 10 minutes post injection.
When Tc-99m pertechnetate is used, 37 to 200 MBq of sodium Tc-99m pertechnetate are injected and neck and thorax images are acquired 30 minutes later. After image acquisition, 185 - 740 MBq of Tc-99m sestamibi are injected and images acquired 10 minutes post injection.
If the double phase technique is used, 370 to 740 MBq of Tc-99m sestamibi are injected and the first neck and thorax image is obtained 10 minutes later. After a wash-out period of 1 to 2 hours, neck and thorax imaging is again performed.

Paediatric population
The use of PoltechMIBI in paediatric patients has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. Safety and efficacy in children and adolescents below the age of 18 have not been fully established.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Pregnancy, see section 4.6.

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.
In patient with reduced kidney function, careful consideration of the indication is required since an increased radiation exposure is possible in these patients.

In patients with reduced hepatobiliary function, a very careful consideration is required since an increased radiation exposure is possible in these patients.

Paediatric population
Paediatric population, see section 4.2.

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 study in order to reduce radiation exposure.
No data concerning the diagnostic efficacy in suspected recurrency or metastatic disease of breast cancer are available.
In myocardial scintigraphy investigations under stress conditions, the general contraindications and precautions associated with the induction of ergometric or pharmacological stress should be considered.

Because of potential tissue damage extravasal injection of this radioactive product has to be strictly avoided.

Close contact with infants should be restricted during 24 hours after product administration.

Specific warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially "sodium free".

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed and no interactions have been described to date. However, medicinal products which affect myocardial function and/or blood flow may cause false negative results in the diagnosis of coronary arterial disease. For this reason, concomitant medication should be taken into consideration when interpreting the results of the scintigraphic examination.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy
Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and the foetus.

The anticipated dose to the uterus from a 740 MBq rest injection would be 5.8 mGy. A radiation dose above 0.5 mGy (approximately equivalent to that exposure from annual background radiation) could potentially result in risk to the foetus. It is therefore not recommended in women known to be pregnant.

Breast-feeding
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk.

If the administration is considered necessary, breastfeeding should be interrupted for 24 hours and the expressed feeds discarded. It is usual to advise that breastfeeding can be restarted when the radioactivity level in the milk will not result in a radiation dose to the child greater than 1 mSv. Close contact with infants should be restricted during this period.

4.7 Effects on ability to drive and use machines

Effects on the ability to drive and use machines have not been described.

4.8 Undesirable effects

For each patient, exposure to ionising radiation must be justified 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.
The frequency of occurrence of the adverse reactions reported after technetium Tc-99m sestamibi administration is presented in the table below.

MedDRA frequency convention:
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)
Frequency not known (cannot be estimated from the available data)

Cardiac disorders Uncommon Rare	 Chest pain/angina pectoris, abnormal ECG. Arrhytmia.
Congenital, familial and genetic disorders Frequency not known	 Hereditary defects.
Nervous system disorders Common Uncommon Rare	 Metallic or bitter taste. Transient headache. Dizziness, seizure, syncope, hypoaesthesia and paraesthesia.
Gastrointestinal disorders Common Uncommon Rare	 Dry mouth. Nausea. Abdominal pain. Dyspepsia.
Skin and subcutaneous tissue disorders Rare Frequency not known	 Allergic skin and mucosa reactions with exanthema (pruritus, urticaria, oedema). Non-itching rash.
Musculoskeletal and connective tissue disorders Rare	 Transient arthritic-like pain.
Neoplasms benign, malignant and unspecified (including cysts and polyps) Frequency not known	 Cancer induction.
Vascular disorders Rare	 Flushing, vasodilation.
General disorders and administration site conditions Rare	 Injection site inflammation. Fever, fatigue.
Immune system disorders Rare	 Severe hypersensitivity reactions such as dyspnoea, hypotension, bradycardia, asthenia and vomiting (usually within two hours of administration), angioedema.

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 reactions are expected to occur with a low probability. For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (effective dose/EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.
Adverse reactions may be reported to Marketing Authorisation Holder.

4.9 Overdose

In the event of administration of a radiation overdose with technetium Tc-99m sestamibi the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and defecation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
diagnostic radiopharmaceuticals,
technetium (Tc-99m) compounds.
ATC code: V 09G A01

At the chemical concentrations used for diagnostic examinations technetium Tc-99m sestamibi does not appear to have any pharmacodynamic activity. After reconstitution with sodium (Tc-99m) pertechnetate solution for injection, the following complex forms (technetium Tc-99m sestamibi):

$Tc\text{-}99m\ (MIBI)_6^+$

Where: MIBI = 2-methoxyisobutylisonitrile

Technetium Tc-99m sestamibi, when administered in usual activities and by the usual way, has no pharmacodynamic effects detectable clinically.

Tissue uptake of Tc-99m sestamibi depends primarily on the vascularisation, which is generally increased in tumour tissue. Due to its lipophilicity and its positive charge, the Tc-99m sestamibi complex crosses the cell membrane and concentrates in the most negatively charged compartment of the cell, the mitochondria.

Cardiac imaging
Technetium Tc-99m sestamibi binds to the mitochondrial membrane and an intact mitochondrial membrane potential is important for intracellular binding.

The uptake of technetium Tc-99m sestamibi in the myocardium is proportional to blood flow in the physiologic flow range. The rate of passive uptake is determined by the membrane permeability of the drug and the surface area of the vascular beds to which it is exposed. Since the radiotracer enters the cell via diffusion, it will underestimate blood flow at high flow rates (> 2.0 ml/g/min.).

When coronary flow varied from 0.52 to 3.19 ml/g/min., myocardial uptake for technetium Tc-99m sestamibi averages 0.38 ± 0.09 of injected activity. Technetium Tc-99m sestamibi from the blood is rapidly distributed into the tissue. Five minutes after injection only about 8 percent of the injected dose is still in the circulation.

Technetium Tc-99m sestamibi undergoes minimal redistribution over time. This may impact on lesion detection as the differential washout between the normal and ischemic myocardium may result in a reduction in defect size or severity with time.

Breast imaging
The cellular concentration of technetium Tc-99m sestamibi was demonstrated to be increased in mammary tumour tissue probably because of the high content of mitochondria in tumour cells and the high membrane potential of tumour cells.

Several in vitro studies demonstrated that technetium Tc-99m sestamibi is a substrate of P-glycoprotein. A direct correlation between the P-glycoprotein expression and the elimination of technetium Tc-99m sestamibi from tumours has been established. The cellular overexpression of P-glycoprotein could result in false negative images of tumours, especially of tumours larger than 1 cm.

Parathyroid imaging
In parathyroid adenomas blood flow and the number of mitochondria are increased. This fact may explain the elevated uptake and retention of technetium Tc-99m sestamibi in parathyroid adenoma.

Accumulation of technetium Tc-99m sestamibi appears to be dependent on blood flow to the tissue, the cell cycle phase (higher uptake in active growing phase), the concentration of technetium Tc-99m sestamibi presented to the tissue and the size of the parathyroid adenoma.

5.2 Pharmacokinetic properties

The cationic complex accumulates in the viable myocardial tissue proportional to the regional coronary blood flow.
Technetium Tc-99m sestamibi from the blood is rapidly distributed into the tissue: 5 minutes after injection only about 8% of the injected dose is still in the circulation.
Animal experiments have shown that uptake is not dependent on the functional capability of the sodium-potassium pump.

Elimination

The major metabolic pathway for clearance of technetium Tc-99m sestamibi is the hepatobiliary system. Activity from the gallbladder appears in the intestine within one hour of injection. About twenty-seven percent of the injected dose is cleared through renal elimination after 24 hours and approximately thirty-three percent of the injected dose is cleared through the faeces in 48 hours. At five minutes post injection about 8% of the injected dose remains in the circulation.

Half-life

The biological myocardial $T_{½}$ is approximately seven (7) hours at rest and at stress conditions. The effective $T_{½}$ (including biological and physical half-lives) is approximately three (3) hours.

Myocardial uptake

Myocardial uptake which is coronary flow dependent is 1.5% of the injected dose at stress and 1.2% of the injected dose at rest.

5.3 Preclinical safety data

In acute intravenous toxicity studies in mice, rats and dogs, the lowest dose of technetium Tc-99m sestamibi that resulted in any deaths was 7 mg/kg (expressed as Cu $(MIBI)_4$ BF_4 content) in female rats.
This corresponds to 500 times the maximal human dose (MHD) of 0.014 mg/kg for adults (70 kg).
Neither rats nor dogs exhibited treatment related effects at technetium Tc-99m sestamibi doses of 0.42 mg/kg (30 times MHD) and 0.07 mg/kg (5 times MHD) respectively for 28 days.
Studies on reproductive toxicity have not been conducted. Cu $(MIBI)_4$ BF_4 showed no genotoxic activity in the Ames, CHO/HPRT and sister chromatid exchange tests. At cytotoxic concentrations, an increase in chromosome aberration was observed in the in vitro human lymphocyte assay. No genotoxic activity was observed in the in vivo mouse micronucleus test at 9 mg/kg. Studies to assess the carcinogenic potential of technetium Tc-99m sestamibi have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous chloride dihydrate
L-cysteine hydrochloride monohydrate
Sodium citrate dihydrate
D-mannitol

6.2 Incompatibilities

The technetium labelling reactions involved depend on maintaining the stannous level in the reduced state. Hence, sodium (Tc-99m) pertechnetate solution for injection, containing oxidants should not be used.

6.3 Shelf life

Kit - 1 year.
After reconstitution and radiolabelling, technetium Tc-99m sestamibi can be used up to 12 hours stored below 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C- 8°C).
During transportation (not longer than 7 days) up to 35°C. For storage conditions after reconstitution of the medicinal product, see section 6.3.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

10 ml glass vials, type I glass (Ph. Eur.) sealed with rubber stopper and an aluminium crimp cap. Vials are packed in cardboard boxes and pack size of 3 or 6 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General warning

This radiopharmaceutical should be received, used and administered only by authorized 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 organisation. 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. Contents of the vial are intended only for use in the preparation of technetium Tc-99m sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure. The content of the kit before extemporary preparation is not radioactive. However, after sodium (Tc-99m) pertechnetate solution for injection 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 spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
See section 12 for instructions for preparation of radiopharmaceuticals.

7. MARKETING AUTHORISATION HOLDER

Narodowe Centrum Badań Jądrowych
ul. Andrzeja Sołtana 7
05-400 Otwock
Poland
Tel.: +48 22 7180700
Fax: +48 22 7180350
e-mail: polatom@polatom.pl

8. MARKETING AUTHORISATION NUMBER

R/3269

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

14.02.1992/22.12.1999/05.02.2005/29.10.2008/ 09.07.2013

10. DATE OF REVISION OF THE TEXT

April 2016

11. DOSIMETRY

Technetium (Tc-99m) is produced by means of a $^{99}Mo/^{99m}Tc$-generator and decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6.02 hours to technetium (Tc-99) which, in view of its long half-life of 2.13 x 10^5 years can be regarded as quasi stable. The projected radiation doses to organs and tissues of a patient of average weight (70 kg) after intravenous injection of technetium Tc-99m sestamibi are given below.
The data are from ICRP 80 and are calculated according to the following assumptions: after intravenous injection the substance is rapidly cleared from the blood and accumulates mainly in muscular tissues (including heart), liver, kidneys and a smaller amount in salivary glands and thyroid. When the substance is injected in conjunction with a stress test, there is a considerable increase of the uptake in organs and tissues. The substance is excreted by the liver and the kidneys in proportions 75% and 25%, respectively.

Organ	Absorbed dose per unit activity administered [mGy/MBq] (resting test)				
	Adults	15 years	10 years	5 years	1 year
Adrenals	0.0075	0.0099	0.015	0.022	0.038
Bladder	0.011	0.014	0.019	0.023	0.041
Bone surfaces	0.0082	0.010	0.016	0.021	0.038
Brain	0.0052	0.0071	0.011	0.016	0.027
Breast	0.0038	0.0053	0.0071	0.011	0.020
Gall bladder	0.039	0.045	0.058	0.100	0.320
Gastrointestinal tract:					
Stomach	0.0065	0.0090	0.015	0.021	0.035
Small intestine	0.015	0.018	0.029	0.045	0.080
Colon	0.024	0.031	0.050	0.079	0.015
(ULI	0.027	0.035	0.057	0.089	0.170)
(LLI	0.019	0.025	0.041	0.065	0.120)
Heart	0.0063	0.0082	0.012	0.018	0.030
Kidneys	0.036	0.043	0.059	0.085	0.150
Liver	0.011	0.014	0.021	0.030	0.052
Lungs	0.0046	0.0064	0.0097	0.014	0.025
Muscles	0.0029	0.0037	0.0054	0.0076	0.014
Oesophagus	0.0041	0.0057	0.0086	0.013	0.023
Ovaries	0.0091	0.012	0.018	0.025	0.045
Pancreas	0.0077	0.010	0.016	0.024	0.039
Red marrow	0.0055	0.0071	0.011	0.030	0.044
Salivary glands	0.014	0.017	0.022	0.015	0.026
Skin	0.0031	0.0041	0.0064	0.0098	0.019
Spleen	0.0065	0.0086	0.014	0.020	0.034
Testes	0.0038	0.0050	0.0075	0.011	0.021
Thymus	0.0041	0.0057	0.0086	0.013	0.023
Thyroid	0.0053	0.0079	0.012	0.024	0.045
Uterus	0.0078	0.010	0.015	0.022	0.038
Remaining organs	0.0031	0.0039	0.0060	0.0088	0.016
Effective dose [mSv/MBq]	**0.0090**	**0.012**	**0.018**	**0.028**	**0.053**

Organ	Absorbed dose per unit activity administered [mGy/MBq] (exercise test)				
	Adults	15 years	10 years	5 years	1 year
Adrenals	0.0066	0.0087	0.013	0.019	0.033
Bladder	0.0098	0.013	0.017	0.021	0.038
Bone surfaces	0.0078	0.0097	0.014	0.020	0.036
Brain	0.0044	0.0060	0.0093	0.014	0.023
Breast	0.0034	0.0047	0.0062	0.0097	0.018
Gall bladder	0.033	0.038	0.049	0.086	0.260
Gastrointestinal tract:					
Stomach	0.0059	0.0081	0.013	0.019	0.032
Small intestine	0.012	0.015	0.024	0.037	0.066
Colon	0.019	0.025	0.041	0.064	0.120
(ULI	0.022	0.028	0.046	0.072	0.130)
(LLI	0.016	0.021	0.034	0.053	0.099)
Heart	0.0072	0.0094	0.010	0.021	0.035
Kidneys	0.026	0.032	0.044	0.063	0.110
Liver	0.0092	0.012	0.018	0.025	0.044
Lungs	0.0044	0.0060	0.0087	0.013	0.023
Muscles	0.0032	0.0041	0.0060	0.0090	0.017
Oesophagus	0.0040	0.0055	0.0080	0.012	0.023
Ovaries	0.0081	0.011	0.015	0.023	0.040
Pancreas	0.0069	0.0091	0.014	0.021	0.035
Red marrow	0.0050	0.0064	0.0095	0.013	0.023
Salivary glands	0.0092	0.011	0.0015	0.0020	0.0029
Skin	0.0029	0.0037	0.0058	0.0090	0.017
Spleen	0.0058	0.0076	0.012	0.017	0.030
Testes	0.0037	0.0048	0.0071	0.011	0.020
Thymus	0.0040	0.0055	0.0080	0.012	0.023
Thyroid	0.0044	0.0064	0.0099	0.019	0.035
Uterus	0.0072	0.0093	0.014	0.020	0.035
Remaining organs	0.0033	0.0043	0.0064	0.0098	0.018
Effective dose [mSv/MBq]	**0.0079**	**0.010**	**0.016**	**0.023**	**0.045**

Myocardial perfusion scintigraphy

The effective doses calculated for a 2-day-protocol resulting from the administration of the activity of 600 - 900 MBq at stress and 600 - 900 MBq at rest range from 10.1 mSv to 15.2 mSv.

The effective doses calculated for a 1-day-protocol resulting from the administration of the activity of 400 - 500 MBq for the first injection and 1000 - 1500 MBq for the second injection range from 11.5 mSv to 17.5 mSv.

Diagnosis of myocardial infarction

The effective doses resulting from the administration of the activity of 400 - 900 MBq, range from 3.6 mSv to 8.1 mSv.

Assessment of global ventricular function and/or regional wall motion

The effective doses resulting from the administration of the activity of 600 - 800 MBq at rest, range from 5.4 mSv to 7.2 mSv. The effective doses resulting from the administration of the activity of 600 - 800 MBq at stress, range from 4.7 mSv to 6.3 mSv.

Breast imaging

The effective doses resulting from the administration of the activity of 740 - 1100 MBq, range from 6.7 mSv to 9.9 mSv.

Parathyroid imaging

The effective doses resulting from the administration of the activity of 185 - 925 MBq, the range from 1.7 mSv to 8.3 mSv.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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. As with any pharmaceutical product, if at any time in the preparation of this product the integrity of this vial is compromised, the product should not be used. Therefore, prior to the radiolabelling procedure carefully inspect the vial for the presence of damage, in particular cracks. Do not use a damaged vial as it may break during heating.

Instructions for preparation of technetium Tc-99m sestamibi

A. Boiling procedure

Preparation of technetium Tc-99m sestamibi is to be done according to the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure.
2. Place the vial in a suitable radiation lead shield appropriately labelled with date, time of preparation, volume and activity.
3. With a sterile lead-shielded syringe (piercing the rubber stopper) introduce 1-5 ml eluate of sodium (Tc-99m) pertechnetate solution with the radioactivity of maximum 11GBq (or the eluate volume with the desired radioactivity adjusted with physiological saline solution) into a vial in the lead shield.
   Not less than 5 ml sodium (Tc-99m) pertechnetate solution will be use for the maximum activity of 11 GBq.
4. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
5. Shake the content of the vial until complete dissolution (about 1 min).
6. Remove the vial from the lead shield and place **upright** in an appropriately shielded boiling water bath, such that while boiling do not allow contact between boiling water and the aluminium cap and boil for 10-12 minutes. Timing for the 10-12 minutes commences as soon as the water **begins to boil** again.

Note: The vial **must** remain upright during the boiling step. Use a water bath where the stopper will be above the level of the water.

7. Remove the vial from the water bath, put into a lead container and allow to cool for fifteen minutes.
8. Inspect visually for the absence of particulate matter and discoloration prior to administration.
9. Aseptically withdraw material using a sterile shielded syringe. Use within twelve (12) hours of preparation.
10. Radiochemical purity should be checked prior to patient administration according to the Radio-TLC Method as detailed below.

Note: The potential for cracking and significant contamination exists whenever vials containing radioactive material are heated.

B. Thermal Cycler procedure

Preparation of technetium Tc-99m sestamibi is to be done according to the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure.
2. Place the vial in a suitable radiation lead shield appropriately labelled with date, time of preparation, volume and activity.
3. With a sterile lead-shielded syringe (piercing the rubber stopper) introduce 1-5 ml eluate of sodium (Tc-99m) pertechnetate solution with the radioactivity of maximum 11GBq (or the eluate volume with the desired radioactivity adjusted with physiological saline solution) into a vial in the lead shield. Not less than 5 ml sodium (Tc-99m) pertechnetate solution will be use for the maximum activity of 11 GBq.
4. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
5. Shake the content of the vial until complete dissolution (about 1 min).
6. Place the shield in the sample block. While slightly pressing downwards, give the shield a quarter turn to make certain there is a firm fit between the shield and the sample block.
7. Press the proceed button to initiate the program (the thermal cycler automatically heats and cools the vial and contents).
   Please see the Manual Instruction for further details.
8. Inspect visually for the absence of particulate matter and discoloration prior to administration.
9. Aseptically withdraw material using a sterile shielded syringe. Use within twelve (12) hours of preparation.
10. Radiochemical purity should be checked prior to patient administration according to the Radio-TLC Method as detailed below.

Radio-TLC Method for the Quantification of technetium Tc-99m sestamibi

1. Materials

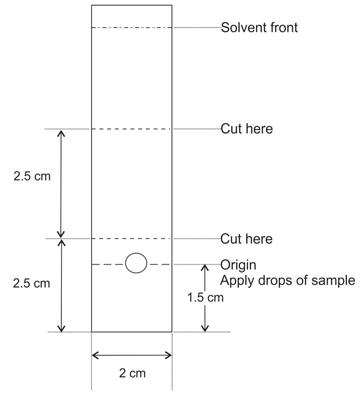
1.1. Neutral Aluminium Oxide type T on aluminium foil plate.
1.2. Ethanol > 95%.
1.3. The suitable radiation detector.
1.4. Small chromatographic chamber.

2. Procedure

2.1. Apply 2-5 µl of the examined solution about 1.5 cm from the bottom of a 2 cm x 8 cm chromatographic plate.
2.2. Put the plate in the chromatographic chamber containing approximately 1 cm high layer of absolute ethanol.
2.3. Develop the chromatogram until the solvent front moves about 6 cm from the starting line (for approximately 10 min.).
2.4. Remove the plate and allow it to air-dry.
2.5. Determine the radioactivity distribution on the plate by scanning the chromatogram with a suitable radiation detector or cut the plate as shown below (three pieces) and measure each piece activity with an appropriate radiation detector.
2.6. Identify radioactivity spots according to their R_f value:
- reduced and/or hydrolysed forms of Tc-99m remain on the starting line R_f = 0.0-0.1
- free, unbound pertechnetate $^{99m}TcO_4^-$ migrates with the solvent R_f = 0.4-0.7
- Tc-99m sestamibi complex migrates with the solvent front R_f = 0.8-1.0

2.7. Calculate the % radiochemical purity as:
% technetium (Tc-99m) sestamibi =
Activity of the upper part (R_f = 0.8-1.0) /
Activity sum of all parts and multiplied by 100
2.8. % technetium (Tc-99m) sestamibi should be ≥ 94%; otherwise the preparation should be discarded.

Note: Do not use material if the radiochemical purity is less than 94%.



After reconstitution the container and any unused contents should be disposed of in accordance with local requirements for radioactive materials.

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