**SUMMARY OF PRODUCT CHARACTERISTICS**
**for**
**Medi-MIBI, kit for radiopharmaceutical preparation**

**1. NAME OF THE MEDICINAL PRODUCT**
Medi-MIBI

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each vial contains 0.5 mg [tetrakis (1 isocyanide-2-methoxy-2-methylpropyl-)copper(I)] tetrafluoroborate.
The radionuclide is not part of the kit.
Excipient with known effect:
Sodium Chloride 13.5 mg
For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**
Kit for radiopharmaceutical preparation.
Lyophilized, white powder.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**
This medicinal product is for diagnostic use only. This is indicated for adults. For paediatric population see section 4.2.
After radiolabelling with sodium pertechnetate (99mTc) solution, the solution of technetium (99mTc) sestamibi obtained is indicated for:
• Myocardial perfusion scintigraphy for the detection and localisation of coronary artery disease (angina pectoris and myocardial infarction)
• Assessment of global ventricular function. First-pass technique for determination of ejection fraction and/or ECG-triggered, gated SPECT for evaluation of left ventricular ejection fraction, volumes and regional wall motion.
• Scintimammography for the detection of suspected breast cancer when mammography is equivocal, inadequate or indeterminate.
• Localisation of hyperfunctioning parathyroid tissue in patients with recurrent or persistent disease in both primary and secondary hyperparathyroidism, and in patients with primary hyperparathyroidism scheduled to undergo initial surgery of the parathyroid glands.

**4.2 Posology and method of administration**
Posology
*Adults and elderly population*
Posology may vary depending on gamma camera characteristics and reconstruction modalities. The injection of activities greater than local DRLs (Diagnostic Reference Levels) should be justified.
The recommended activity range for intravenous administration to an adult patient of average weight (70 kg) is for:
*Diagnosis of reduced coronary perfusion and myocardial infarction*
400 – 900 MBq
The recommended activity range for diagnosis of ischaemic heart disease according to the European procedural guideline is
– Two-day protocol: 600–900 MBq/study
– One-day protocol: 400–500 MBq for the first injection, three times more for the second injection.
Not more than a total of 2000 MBq should be administered for a one-day protocol and 1800 MBq for a two-day-protocol. For a one day protocol, the two injections (stress and rest) should be done at least two hours apart but may be performed in either order. After the stress injection, exercise should be encouraged for an additional one minute (if possible).
For diagnosis of myocardial infarction one injection at rest is usually sufficient.
For diagnosis of ischaemic heart disease two injections (stress and rest) are required in order to differentiate transiently from persistently reduced myocardial uptake.
*Assessment of global ventricular function*
600-800 MBq injected as a bolus.
*Scintimammography*
700 - 1000 MBq injected as a bolus usually in the arm opposite to the lesion.
*Localisation of hyperfunctioning parathyroid tissue*
200 - 700 MBq injected as a bolus. The typical activity is between 500-700 MBq.
Posology may vary depending on gamma camera characteristics and reconstruction modalities.
The injection of activities greater than local DRLs (Diagnostic Reference Levels) should be justified.
*Renal impairment*
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.
*Hepatic impairment*
In general, activity selection for patients with a decreased hepatic function should be cautious, usually starting at the low end of the dosing range.
*Paediatric population*
The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activities to be administered to children and adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent multiples given in the table below.
A[MBq]Administered = Baseline Activity × Multiple
The baseline activity is 63 MBq as a cancer seeking agent. For cardiac imaging, the minimum and maximum baseline activities are 42 and 63 MBq, respectively, for the two-day protocol cardiac scan both at rest and stress. For the one-day cardiac imaging protocol, the baseline activity is 28 MBq at rest and 84 MBq at stress. The minimum activity for any imaging study is 80 MBq.

| **Weight [kg]** | Multiple | **Weight [kg** | Multiple | **Weight [kg]** | Multiple |
|---|---|---|---|---|---|
| **3** | 1 | 22 | 5.29 | **42** | 9.14 |
| **4** | 1.14 | **24** | 5.71 | **44** | 9.57 |
| **6** | 1.71 | **26** | 6.14 | **46** | 10.00 |
| **8** | 2.14 | **28** | 6.43 | **48** | 10.29 |
| **10** | 2.71 | **30** | 6.86 | **50** | 10.71 |
| **12** | 3.14 | **32** | 7.29 | **52-54** | 11.29 |
| **14** | 3.57 | **34** | 7.72 | **56-58** | 12.00 |
| **16** | 4.00 | **36** | 8.00 | **60-62** | 12.71 |
| **18** | 4.43 | **38** | 8.43 | **64-66** | 13.43 |
| **20** | 4.86 | **40** | 8.86 | **68** | 14.00 |

Method of administration
For intravenous use.
Because of potential tissue damage, extravasal injection of this radioactive product has to be strictly avoided.
For multidose use.
*Precautions to be taken before handling or administration of the medicinal product*
This medicinal product should be reconstituted before administration to the patient. For instructions on reconstitution and control of the radiochemical purity of the medicinal product before administration, see section 12.
For patient preparation, see section 4.4.
*Image acquisition*
*Cardiac imaging*
Imaging should begin approximately after 30-60 min after injection to allow for hepatobiliary clearance. Longer delay can be required for resting images and for stress with vasodilatators alone because of the risk of higher subdiaphragmatic technetium (99mTc) 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. Test may be done in a one day or two days protocol.
Preferably tomographic imaging (SPECT) with or without ECG gating should be performed.
*Scintimammography*
Breast imaging is optimally initiated 5 to 10 minutes post injection with the patient in the prone position with breast freely pendant.
The product is administered in an arm vein contralateral to the breast with the suspected abnormality. If the disease is bilateral, the injection is ideally administered in a dorsal vein of the foot.
Conventional gamma camera
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.
Detector dedicated to breast imaging
In case a detector dedicated to breast imaging is used, a relevant machine-specific protocol must be followed to obtain the best possible imaging performance.
*Parathyroid imaging*
Parathyroid image acquisition depends on the protocol chosen. The most used studies are either the subtraction and/or the dual-phase techniques, which can be performed together.
For the subtraction technique either sodium iodide ($^{123}$I) or sodium pertechnetate ($^{99m}$Tc) can be used for imaging for the thyroid gland since these radiopharmaceuticals are trapped by functioning thyroid tissue. This image is subtracted from the technetium ($^{99m}$Tc) sestamibi image, and pathological hyperfunctioning parathyroid tissue remains visible after subtraction. When sodium iodide ($^{123}$I) is used, 10 to 20 MBq are orally administered. Four hours after the administration, neck and thorax images may be obtained. After sodium iodide ($^{123}$I) image acquisition, 200 to 700 MBq of technetium ($^{99m}$Tc) sestamibi are injected and images are acquired 10 minutes post injection in double acquisition with 2 peaks of gamma energy (140 keV for technetium ($^{99m}$Tc) and 159 keV for iodine ($^{123}$I)). When sodium pertechnetate ($^{99m}$Tc) is used, 40-150 MBq are injected and neck and thorax images are acquired 30 minutes later. Then 200 to 700 MBq of technetium ($^{99m}$Tc) sestamibi are injected and a second acquisition of images is acquired 10 minutes later.
For the dual phase technique is used, 400 to 700 MBq of technetium ($^{99m}$Tc) sestamibi are injected and the first neck and mediastinum image is obtained 10 minutes later. After a wash-out period of 1 to 2 hours, neck and mediastinum imaging is again performed.
The planar images may be complemented by early and delayed SPECT or SPECT/CT.

**4.3 Contraindications**
Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
In myocardial scintigraphy investigations under stress conditions, the general contraindications associated with the induction of ergometric or pharmacological stress should be considered.

**4.4 Special warnings and precautions for use**
Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occurs, 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.
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 or hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible (see section 4.2).
Paediatric population
For information on the use in paediatric population, see section 4.2.
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).
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.
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 ($^{99m}$Tc) sestamibi resulting in less liver activity in the image.
Interpretation of technetium ($^{99m}$Tc) sestamibi images
Interpretation of scintimammography
Breast lesions less than 1 cm in diameter may not all be detected with scintimammography as the sensitivity of technetium ($^{99m}$Tc) sestamibi for the detection of these lesions is low. A negative examination does not exclude breast cancer especially in such a small lesion.
After the procedure
Close contact with infants and pregnant women should be restricted during the initial 24 hours following the injection.
Specific warnings
In myocardial scintigraphy investigations under stress conditions, the general contraindications and precautions associated with the induction of ergometric or pharmacological stress should be considered.
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'. Depending on the time when you administer the injection, the content of sodium given to the patient may in some cases be greater than 1 mmol. This should be taken into account in patient on low sodium diet.
For precautions with respect to environmental hazard see section 6.6.

**4.5 Interaction with other medicinal products and other forms of interaction**
Medicinal products which affect myocardial function and/or blood flow may cause false negative results in the diagnosis of coronary arterial disease. Particularly beta-blockers and calcium antagonists reduce oxygen consumption and thus also affect perfusion and beta-blockers inhibit the increase of heart frequency and blood pressure under stress. For this reason, concomitant medicinal product should be taken into consideration when interpreting the results of the scintigraphic examination. The recommendations of the applicable guidelines on ergometric or pharmacological stress tests should be followed.
When the subtraction technique is used for imaging of hyperfunctioning parathyroid tissue, recent use of iodine containing radiologic contrast media, medicinal products used to treat hyper- or hypothyroidism or of several other medicinal products is likely to decrease the quality of thyroid imaging and even makes subtraction impossible. For a complete list of possibly interacting medicinal products refer to the SmPCs of sodium iodide ($^{123}$I) or sodium pertechnetate ($^{99m}$Tc).
Paediatric population
Interaction studies have only been performed in adults.

**4.6 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 dose 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 foetus.
Breastfeeding
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.
Close contact with infants should be restricted during the initial 24 hours following injection.
Fertility
No studies on fertility have been performed.

**4.7 Effects on ability to drive and use machines**
Medi-MIBI has no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**
The following table presents how the frequencies are reflected in this section:

| |
|---|
| 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) |
| Not known (cannot be estimated from the available data) |

*Immune system disorders*
Rare: Severe hypersensitivity reactions such as dyspnoea, hypotension, bradycardia, asthenia and vomiting (usually within two hours of administration), angioedema. Other hypersensitivity reactions (allergic skin and mucosa reactions with exanthema (pruritus, urticaria, oedema), vasodilatation).
Very rare: Other hypersensitivity reactions have been described in predisposed patients.
*Nervous system disorders*
Uncommon: Headache
Rare: Seizures (shortly after administration), syncope.
*Cardiac disorders*
Uncommon: Chest pain/angina pectoris, abnormal ECG.
Rare: Arrhythmia.
*Gastrointestinal disorders*
Uncommon: Nausea
Rare: Abdominal pain.
*Skin and subcutaneous tissue disorders*
Rare: local reactions at the injection site, hypoaesthesia and paraesthesia, flushing
Not known: Erythema multiform.
*General disorders and administration site conditions*
Common: Immediately after injection, a metallic or bitter taste, partly in combination with dry mouth and an alteration in the sense of smell may be observed.
Rare: Fever, fatigue, dizziness, transient arthritic-like pain, dyspepsia.
*Other disorders*
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 16.4 mSv when the maximal recommended activity of 2000 MBq (500 at rest and 1500 MBq at stress) for a 1-day-protocol 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

**4.9 Overdose**
In the event of administration of a radiation overdose with technetium ($^{99m}$Tc) 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 defaecation. It might be helpful to estimate the effective dose that was applied.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: diagnostic radiopharmaceuticals, Technetium ($^{99m}$Tc) compounds, ATC code: V09GA01.
Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations, technetium ($^{99m}$Tc) sestamibi solution does not appear to have any pharmacodynamic activity.

**5.2 Pharmacokinetic properties**
After reconstitution with sodium pertechnetate ($^{99m}$Tc), the following technetium ($^{99m}$Tc) sestamibi complex is formed:
$[^{99m}Tc\ (MIBI)_6]^+$ Where : MIBI = 2-methoxyisobutylisonitrile
Biodistribution
Technetium ($^{99m}$Tc) sestamibi from the blood is rapidly distributed into the tissue: 5 minutes after injection only about 8% of the injected dose remains in the blood pool. In physiological distribution, evident concentration of technetium ($^{99m}$Tc) sestamibi can be seen in vivo in several organs. In particular, normal tracer uptake is evident in the salivary glands, thyroid, myocardium, liver, gallbladder, small and large intestine, kidneys, bladder, choroid plexuses and skeletal muscles, occasionally in the nipples. Faint homogeneous uptake in the breast or axilla is normal.
Myocardial perfusion scintigraphy
Technetium ($^{99m}$Tc) sestamibi is a cationic complex which diffuses passively through the capillary and cell membrane. Within the cell it is localised in the mitochondria, where it is trapped, and retention is based on intact mitochondria, reflecting viable myocytes. After intravenous injection, it is distributed within the myocardium according to myocardial perfusion and viability. 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. Irreversibly damaged cells however do not take up technetium ($^{99m}$Tc) sestamibi. The myocardial extraction level is reduced by hypoxia. It has very little redistribution and so separate injections are required for stress and resting studies.
Scintimammography
The tissue uptake of technetium ($^{99m}$Tc) sestamibi depends primarily on the vascularisation which is generally increased in tumor tissue. Technetium (99mTc) sestamibi accumulates in various neoplasms and most markedly in mitochondria. Its uptake is related to increased energy-dependent metabolism and cell proliferation. Its cellular accumulation is reduced when multidrug resistance proteins are overexpressed.
Parathyroid imaging of hyperfunctioning tissue
Technetium ($^{99m}$Tc) sestamibi localises in both parathyroid tissue and functioning thyroid tissue but usually washes out of normal thyroid tissue more rapidly than out of abnormal parathyroid tissue.
Elimination
Elimination of technetium ($^{99m}$Tc) sestamibi occurs mostly through the kidneys and the hepatobiliary system. Activity of technetium ($^{99m}$Tc) sestamibi from the gallbladder appears in the intestine within one hour of injection. About 27% of the injected dose is cleared through renal elimination after 24 hours and approximately 33% of the injected dose is cleared through the faeces in 48 hours. The pharmacokinetics in patients with renal or hepatic impairment has not been characterised.

Half-life
The biological myocardial half-life of technetium ($^{99m}$Tc) sestamibi is approximately 7 hours at rest and stress. The effective half-life (which includes biological and physical half-lives) is approximately 3 hours for the heart and approximately 30 minutes for the liver.

**5.3 Preclinical safety data**

In acute intravenous toxicity studies in mice, rats and dogs, the lowest dose of the reconstituted kit that resulted in any deaths was 7 mg/kg (expressed as Cu (MIBI)4 BF4 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 reconstituted kit doses of 0.42 mg/kg (30 times MHD) and 0.07 mg/kg (5 times MHD) respectively for 28 days. At repeated dose administration, the first toxicity symptoms appeared during the administration of 150 times the daily dose during 28 days.
Extravasation administration in animals showed acute inflammation with oedema and haemorrhages at the injected site.
Studies on reproductive toxicity have not been conducted.
$Cu(MIBI)_4BF_4$ 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 the radiopharmaceutical kit have not been conducted.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Stannous (II) Chloride Dihydrate
Tetrasodium Pyrophosphate Decahydrate
L-Cysteine hydrochloride monohydrate
Glycine
Sodium Chloride

**6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

**6.3 Shelf life**

*30 months*
After radiolabelling: 8 hours. Do not store above 25 °C after radiolabelling.

**6.4 Special precautions for storage**

Do not store above 25°C. Keep the vials in the outer carton in order to protect from light.
For storage conditions after radiolabelling 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**

8 ml, colourless, Type I, borosilicat glass vials, closed with chlorobutyl rubber stopper and plastic-aluminium caps (polypropylene-aluminium caps) with turned up edge.
Pack sizes:

1 pack contains 6 vials.
Hospital packs: Bundle pack of 2 packs of 6 vials.
Bundle pack of 4 packs of 6 vials.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

General warnings
Radiopharmaceuticals should 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 competent official organisation.
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) sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.
For instructions on extemporary preparation of the medicinal product before administration, see section 12.
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 extemporary preparation is not radioactive. However, after sodium pertechnetate ($^{99m}$Tc), 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 or any other biological fluids. 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.

## 7. MARKETING AUTHORISATION HOLDER

RADIOPHARMACY Laboratory Ltd.
2040 Budaörs, Gyár u. 2
Hungary

## 8. MARKETING AUTHORISATION NUMBER(S)

DK R 02236

## 9. DATE OF FIRST AUTHORISATION

14 March 2008

## 10. DATE OF REVISION OF THE TEXT

30 October 2015

## 11. 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 140 keV and a half-life of 6.02 hours to technetium ($^{99}$Tc) which, in view of its long half-life of 2.13 x 105 years, can be regarded as quasi stable.
The data listed below are from ICRP 80 and are calculated according to the following assumptions. After intravenous injection, the substance is rapidly cleared from the blood and taken up predominantly mainly in muscular tissues (including heart), liver, and kidneys, with 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 heart and skeletal muscles, with a correspondingly lower uptake in all other organs and tissues. The substance is excreted by the liver and kidneys in the proportions 75% and 25%, respectively.

**Absorbed dose per unit activity administered (mGy/MBq) (Resting subject)**

| Organ | Adult | 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 | 0.1 | 0.32 |
| 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 |
| (Upper large intestine | 0.027 | 0.035 | 0.057 | 0.089 | 0.17) |
| (Lower large intestine | 0.019 | 0.025 | 0.041 | 0.065 | 0.12) |
| Heart | 0.0063 | 0.0082 | 0.012 | 0.018 | 0.030 |
| Kidneys | 0.036 | 0.043 | 0.059 | 0.085 | 0.15 |
| 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** |

**Absorbed dose per unit activity administered (mGy/MBq) (Exercise)**

| Organ | Adult | 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 | 0.024 | 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 | 0.26 |
| 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 | 0.12 |
| (Upper large intestine | 0.022 | 0.028 | 0.046 | 0.072 | 0.13) |
| (Lower large intestine | 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 | 0.11 |
| 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** |

The effective dose has been calculated according to a voiding frequency of 3.5 hours in adults.

*Cardiac imaging*
The effective dose resulting from the administration of a maximal recommended activity of 2,000 MBq of technetium ($^{99m}$Tc) sestamibi for an adult weighing 70 kg is about 16.4 mSv if implementing the one-day protocol with administration of 500 MBq at rest and 1,500 MBq at exercise.
For this administered activity of 2,000 MBq the typical radiation dose to the target organ heart is 14 mGy and the typical radiation doses to the critical organs gall bladder, kidneys and upper large intestine are 69, 57 and 46.5 mGy, respectively.
The effective dose resulting from the administration of a maximal recommended activity of 1,800 MBq (900 MBq at rest and 900 MBq at exercise) of technetium ($^{99m}$Tc) sestamibi for a two-day protocol for an adult weighing 70 kg is about 15.2 mSv.
For this administered activity of 1,800 MBq the typical radiation dose to the target organ heart is 12.2 mGy and the typical radiation doses to the critical organs gall bladder, kidneys and upper large intestine are 64.8, 55.8 and 44.1 mGy, respectively.
*Scintimammography*
The effective dose resulting from the administration of a maximal recommended activity of 1,000 MBq of technetium ($^{99m}$Tc) sestamibi for an adult weighing 70 kg is about 9 mSv.
For an administered activity of 1,000 MBq the typical radiation dose to the target organ breast is 3.8 mGy and the typical radiation doses to the critical organs gall bladder, kidneys and upper large intestine are 39, 36 and 27 mGy, respectively.
*Parathyroid imaging*
The effective dose resulting from the administration of a maximal recommended activity of 700 MBq of technetium ($^{99m}$Tc) sestamibi for an adult weighing 70 kg is about 6.3 mSv.
For an administered activity of 700 MBq the typical radiation dose to the target organ thyroide is 3.7 mGy and the typical radiation doses to the critical organs gall bladder, kidneys and upper large intestine are 27.3, 25.2 and 18.9 mGy, respectively.

## 12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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.
Instructions for preparation of technetium ($^{99m}$Tc) sestamibi
Technetium Tc-99m Sestamibi is to be used within eight (8) hours of reconstitution. The vial is reconstituted with a maximum 15 GBq of oxidant-free sterile Tc-99m-Sodium pertechnetate. As with any pharmaceutical product, if at any time in the preparation of this product the integrity of this vial is compromised it should not be used.
Use only eluate from a Tc-99m generator previously eluted within 24 hours. Use only eluate taken from generator less than 2 hours before reconstitution
The labelling of the kit should be made according to either method A or method B.
Method of preparation
**Instructions for Preparation of Technetium Tc-99m Sestamibi**
**A Boiling procedure:**
Preparation of Technetium Tc-99m Sestamibi from the Medi-MIBI 500 micrograms Kit is to be done according to the following aseptic procedure:
1. Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the Medi-MIBI 500micrograms Kit vial and swab the top of the vial closure with alcohol to disinfect the surface.
2. Place the vial in a suitable radiation shield appropriately labelled with date, time of preparation, volume and activity.
3. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc-99m solution (max. 15 GBq –405mCi) in approximately 1 to 5 ml.
4. Aseptically add the Sodium Pertechnetate Tc-99m solution to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
5. Shake vigorously, about 5 to 10 quick upward-downward motions.
6. Remove the vial from the lead shield and place upright in an appropriately shielded and contained boiling water bath, such that the vial is suspended above the bottom of the bath, and boil for 10 minutes. The bath must be shielded. Timing for the 10 minutes commences as soon as the water begins to boil again.
7. 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.
8. Remove the shielded vial from the water bath and allow cooling for fifteen minutes.
9. Inspect visually for the absence of particulate matter and discoloration prior to administration.
10. Aseptically withdraw material using a sterile shielded syringe. Use within eight (8) hours of preparation.
11. Radiochemical purity should be checked prior to patient administration according to the Radio TLC Method or organic solvent extraction method as detailed below.
NOTE: The potential for cracking and significant contamination exists whenever vials containing radioactive material are heated.
Method "B" - Dry Heating procedure
Preparation of Technetium Tc-99m Sestamibi from the Medi-MIBI 500micrograms Kit is to be done according to the following aseptic procedure:
Waterproof gloves should be worn during the preparation procedure. Remove the flip off disc from the Medi-MIBI 500micrograms Kit vial and swab with sanitising wipe the top of the vial closure to disinfect the surface.
Place the vial in a suitable radiation shield appropriately labelled with date, time of preparation, volume and activity.
With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc-99m solution (max. 15 GBq) in volume of 1 to 5 ml.
Aseptically add the Sodium Pertechnetate Tc-99m solution to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
Shake vigorously, about 5 to 10 quick upward-downward motions.
Place the vial in the dry block heaters. While slightly pressing downwards, be sure that there is a firm fit between the vial and the sample block.
Press the button to initiate the heating program. After 10 minutes boiling put vials into vial shield and allows cooling down the room temperature.
Inspect visually by using lead glasses for the absence of particulate matter and discoloration prior to administration.
Aseptically withdraw all the doses with a sterile shielded syringe. Use within 8 hours of preparation.
Radiochemical purity should be checked prior to patient administration according to the radio TLC method and organic solvent extraction method as detailed below.
After reconstitution, store the labelled Medi-MIBI 500micrograms below 25oC and protected from light.
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.
Quality control
Radio-TLC Method for the Quantification of Technetium Tc-99m Sestamibi
1. Materials
1.1. Baker-Flex-Aluminium Oxide plate, # 1 B-F, pre-cut to 2.5 cm x 7.5 cm.
1.2. Ethanol >95%.
1.3. Capintec, or equivalent instrument for measuring radioactivity in the 0.01MBq – 15 GBq range. The resolution value is 0.001MBq.
1.4. 1 ml syringe with a 22-26 gauge needle.
1.5. Small developing tank with cover, (100 ml beaker covered with Parafilm® is sufficient).
2. Procedure
2.1. Pour enough ethanol into the developing tank (beaker) to have a depth of 3-4 mm of solvent. Cover the tank (beaker) with Parafilm® and allow it to equilibrate for approximately 10 minutes.
2.2. Apply 1 drop of ethanol, using a 1 ml syringe with a 22-26 gauge needle on to the Aluminium Oxide TLC plate, 1.5 cm from the bottom. Do not allow the spot to dry.
2.3. Apply 1 drop of the kit solution on top of the ethanol spot. Dry the spot. Do not heat!
2.4. Develop the plate a distance of 5.0 cm from the spot.
2.5. Cut the strip 4.0 cm from the bottom, and measure each piece in your dose calibrator.
2.6. Calculate the % Radiochemical purity as:
% Tc-99m Sestamibi = (Activity top portion)/(Activity both pieces) x 100.
2.7. % Tc-99m Sestamibi should be > 94%; otherwise the preparation should be discarded.
II. Organic solvent extraction method
Materials and equipments
Sodium chloride solution
Chloroform
Vortex Mixer
Capintec, or equivalent instrument for measuring radioactivity in the 0.01MBq – 15 GBq range. The resolution value is 0.001MBq.
Procedure
Add 0.1 ml of the labelled compound into a vial, which contains 3 ml of chloroform and 2.9 ml of saline. Close the vial, mix on a vortex mixer for 1 min., then after wait for separation of phases (1-2 min).
Transfer the top layer (saline) to another vial and measure the activities of both phases (vial of saline and vial of chloroform) in a dose calibrator separately. The lipophilic Tc-99m-MIBI is in the chloroform fraction and the contaminants are in the saline layer.
Calculation
Calculate the percentage of 99mTc-Medi-MIBI:

$$\%\ \text{of lipophilic 99mTc-Medi-MIBI} = \frac{\text{Activity of chloroform fraction}}{\text{Total activity of both fractions}} \times 100$$

**The percentage of radiochemical purity should be not less than 94% within 8 hours**