SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cardiovis 1 mg kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg

[tetrakis (1-isocyanide-2-methoxy-2-methylpropyl) copper(I)] tetrafluoroborate.

The radionuclide is not part of the kit.

Excipient with known effect:

Sodium 0.009 mmol (0.2 mg) per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation

The product is a white, lyophilised 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 (^{99m}Tc) solution, the solution of technetium (^{99m}Tc) 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 instruction on reconstitution and control of 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 vasodilators alone because of the risk of higher subdiaphragmatic technetium (^{99m}Tc) 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 to 150 MBq are injected and neck and thorax images are acquired 30 minutes later. Then, 200 to 700 MBq technetium (^{99m}Tc) sestamibi are injected and a second acquisition of images is acquired 10 minutes later.

If 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 scintimmamography

Breast lesions less than 1cm 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'.

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 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 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 the 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

Cardiovis 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 Yellow Card Scheme.

Website: *www.mhra.gov.uk/yellowcard*

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: V 09G A01

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 tumour tissue. Technetium(^{99m}Tc) 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 (ex-

pressed 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 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)$_4$ 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 the radiopharmaceutical kit 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

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

6.3 Shelf life

1 year

After radiolabelling: Chemical and physical in-use stability has been demonstrated for 12 hours. Do not store above 25°C after radiolabelling.

From a microbiological point of view, unless the method of opening / radiolabelling / dilution precludes the risk of microbiological contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 ºC).
During transportation (not longer than 7 days) up to 35°C.

For storage conditions after radiolabelling of 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 vial (Type I) sealed with a chlorobutyl rubber stopper and an aluminium crimp cap.

Vials are packed in cardboard boxes and pack sizes 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

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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 34397/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: 09/09/2013

10. DATE OF REVISION OF THE TEXT

09/09/2013

11.DOSIMETRY (IF APPLICABLE)

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 10^5 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 the kidneys in proportions 75% and 25%, respectively.

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

Organ	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
(Upper large intestine	0.027	0.035	0.057	0.089	0.170)
(Lower large intestine	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	0.029	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	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
(Upper large intestine	0.022	0.028	0.046	0.072	0.130)
(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	0.110
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**

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.

Before administration, dilution of the labelled product with sodium chloride solution (0.9 %, physiological saline) is possible.

Instructions for preparation of technetium (^{99m}Tc) sestamibi

A) Boiling procedure

Preparation of technetium (^{99m}Tc) sestamibi injection is to be done according to the following aseptic procedure:

- Waterproof gloves should be worn during the preparation procedure
- Place the vial with the lyophilisate in a suitable radiation lead shield appropriately labelled with date, time of preparation, volume and activity.
- With a sterile, lead-shielded syringe (piercing the rubber stopper) introduce 1 – 5 ml eluate of sodium pertechnetate (^{99m}Tc) injection obtained from a radionuclide generator with marketing authorisation with the radioactivity of maximum 11 GBq (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 pertechnetate (^{99m}Tc) injection will be used for the maximum activity of 11 GBq.
- Without withdrawing the needle, remove an equal volume of headspace into the syringe to maintain atmospheric pressure within the vial.
- Shake the content of the vial until complete dissolution (about 1 minute).
- 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.

- Remove the vial from the water bath, put it into a lead container and allow to cool for fifteen minutes.
- Inspect visually for the absence of particulate matter and discoloration prior to administration.
- Aseptically withdraw Technetium (^{99m}Tc) sestamibi injection using a sterile shielded syringe. Use within twelve (12) hours of preparation.
- Radiochemical purity should be checked prior to patient administration according to the Radio TLC Method as detailed below or alternatively according the pharmacopoeia monograph No. 1926 Technetium (^{99m}Tc) sestamibi injection.

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

B) Thermal Cycler procedure

Preparation of technetium (^{99m}Tc) sestamibi injection is to be done according to the following aseptic procedure:

- Waterproof gloves should be worn during the preparation procedure
- Place the vial with the lyophilisate in a suitable radiation lead shield appropriately labelled with date, time of preparation, volume and activity.
- With a sterile lead-shielding syringe (piercing the rubber stopper) introduce 1 - 5 ml eluate of sodium pertechnetate (^{99m}Tc) injection obtained from a radionuclide generator with marketing authorisation with the radioactivity of maximum 11 GBq (or the eluate volume with desired radioactivity adjusted with physiological saline solution) into a vial in the lead shield. Not less than 5 ml sodium pertechnetate (^{99m}Tc) injection will be used for the maximum activity of 11 GBq.
- Without withdrawing the needle, remove an equal volume of headspace into the syringe to maintain atmospheric pressure within the vial.
- Shake the content of the vial until complete dissolution (about 1 minute).
- 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.
- 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.
- Inspect visually for the absence of particulate matter and discoloration prior to administration.
- Aseptically withdraw Technetium (^{99m}Tc) sestamibi injection using a sterile shielded syringe. Use within twelve (12) hours of preparation.
- Radiochemical purity should be checked prior to patient administration according to the Radio TLC Method as detailed below or alternatively according the pharmacopoeia monograph No. 1926 Technetium (^{99m}Tc) sestamibi injection.

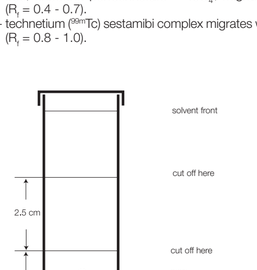
Quality control

Radio-TLC Method for the quantification of technetium (^{99m}Tc) 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

- Apply 2 – 5 µl of the examined solution about 1.5 cm from the bottom of a 2 cm x 8 cm aluminium oxide chromatographic plate.
- Place the plate in the chromatographic chamber containing approximately 1 cm high layer of absolute ethanol
- Develop the chromatogram until the solvent front moves about 6 cm from the starting line (for approximately 10 minutes).
- Remove the plate and allow it to air-dry.
- 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.
- 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).
  - technetium (^{99m}Tc) sestamibi complex migrates with the solvent front (R_f = 0.8 - 1.0).



- Place the vial with the lyophilisate in a suitable radiation lead shield appropriately labelled with date, time of preparation, volume and activity.
- With a sterile lead-shielding syringe (piercing the rubber stopper) introduce 1 - 5 ml eluate of sodium pertechnetate (^{99m}Tc) injection obtained from a radionuclide generator with marketing authorisation with the radioactivity of maximum 11 GBq (or the eluate volume with desired radioactivity adjusted with physiological saline solution) into a vial in the lead shield. Not less than 5 ml sodium pertechnetate (^{99m}Tc) injection will be used for the maximum activity of 11 GBq.
- Without withdrawing the needle, remove an equal volume of headspace into the syringe to maintain atmospheric pressure within the vial.
- Shake the content of the vial until complete dissolution (about 1 minute).
- 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.
- 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.
- Inspect visually for the absence of particulate matter and discoloration prior to administration.
- Aseptically withdraw Technetium (^{99m}Tc) sestamibi injection using a sterile shielded syringe. Use within twelve (12) hours of preparation.
- Radiochemical purity should be checked prior to patient administration according to the Radio TLC Method as detailed below or alternatively according the pharmacopoeia monograph No. 1926 Technetium (^{99m}Tc) sestamibi injection.

- Calculate the % Radiochemical purity as: % Tc-99m Sestamibi = activity of the upper part (R_f = 0.8 - 1.0) divided by the sum of the activity in all parts and multiplied by 100:

$$\% \text{ RCP} = \frac{\text{Act. Upper part}}{\text{Act. Sum of all parts}} \times 100\ \%$$

- % ^{99m}Tc Sestamibi should be ≥ 94%; otherwise the preparation should be discarded.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.