STAMICIS 1 mg
Kit for radiopharmaceutical preparation

SUMMARY OF PRODUCT CHARACTERISTICS

CIS bio international, member of IBA group

T3069nB
01/2010

1. NAME OF THE MEDICINAL PRODUCT

STAMICIS 1 mg kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg Tetrakis (2-methoxyisobutyl isonitrile) copper (I) tetrafluoroborate.

The radioisotope is not part of the kit.

Excipients:
One ml of solution contains 4.5 mg of sodium

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.

After reconstitution with sodium pertechnetate (^{99m}Tc) solution for injection, the solution of technetium (^{99m}Tc) sestamibi obtained is indicated for:

Myocardial perfusion scintigraphy
Detection and localisation of coronary artery disease 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.

Scinti-mammography for the detection of suspected breast cancer
Detection of suspected breast cancer when mammography is equivocal, inadequate or indeterminate.

Localisation of hyperfunctioning parathyroid tissue in patients with recurrent or persistent hyperparathyroidism, and in patients scheduled to undergo surgery of the parathyroid glands.

4.2 Posology and method of administration

This product is only for intravenous injection.
Because of potential tissue damage extravasal injection of this radioactive product has to be strictly avoided.
This medicinal product must be reconstituted before use with sodium pertechnetate (^{99m}Tc) solution for injection. The solution of technetium (^{99m}Tc) sestamibi obtained is a clear and colourless solution , free from visible particles.

For the instruction for preparation and control of radiochemical purity of the radiopharmaceutical, see section 12.

Posology

Adults
The suggested activity range for intravenous use to a patient of average weight (70 kg) is:

Myocardial perfusion scintigraphy: 400-900 MBq.

Assessment of global ventricular function: 600-800 MBq injected as a bolus.
For diagnosis of ischaemic heart disease two injections (stress and rest) are required in order to differentiate transiently from persistently reduced myocardial uptake.

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 may be sufficient.

The injection of activities greater than local DRLs (Diagnostic Reference Levels) should be justified.

Scinti-mammography for the detection of suspected breast cancer: 750-1000 MBq injected as a bolus in the arm opposite to the lesion.

Localisation of hyperfunctioning parathyroid tissue: 200-1000 MBq injected as a bolus (the activity used should in every case be as low as reasonably practical). The typical activity is 740 MBq.

Children and adolescents
Safety and efficacy in children and adolescents below the age of 18 have not been fully established. Alternative techniques which do not involve ionising radiation should be especially considered.
The use technetium (^{99m}Tc) sestamibi 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 for paediatric patients should be modified according to the recommendations of the Paediatric Task Group of the EANM (1990). This activity can be determined from the recommended activity for adults on the basis of body mass, using the following multiplying coefficient:

3 kg = 0.10	12 kg = 0.32	22 kg = 0.50	32 kg = 0.62	42 kg = 0.78	52-54 kg = 0.90
4 kg = 0.14	14 kg = 0.36	24 kg = 0.53	34 kg = 0.64	44 kg = 0.80	56-58 kg = 0.92
6 kg = 0.19	16 kg = 0.40	26 kg = 0.56	36 kg = 0.66	46 kg = 0.82	60-62 kg = 0.96
8 kg = 0.23	18 kg = 0.44	28 kg = 0.58	38 kg = 0.68	48 kg = 0.85	64-66 kg = 0.98
10 kg = 0.27	20 kg = 0.46	30 kg = 0.60	40 kg = 0.70	50 kg = 0.88	68 kg = 0.99

Method of administration and scintigraphic examination

Myocardial perfusion scintigraphy

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.

Imaging should begin approximately after 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 ^{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 according to current international guidelines.

Breast imaging

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.

Breast imaging is optimally initiated 5 to 10 minutes post injection with the patient in the prone position with breast freely pendant. A 10 minute lateral image 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

Acquisition depends on the protocol chosen. The most used studies are either the dual-phase and/or the subtraction techniques, which can be performed together.

- Subtraction technique of the activity of the thyroid:

In order to visualize the parathyroid, either pertechnetate(^{99m}Tc) or iodine (^{123}I) can be given first, followed by technetium (^{99m}Tc) sestamibi, or technetium (^{99m}Tc) sestamibi can be given first, followed by pertechnetate (^{99m}Tc).

When iodine (^{123}I) is used, 10 to 20 MBq of oral iodine (^{123}I) are administered. Four hours after the administration of ^{123}I, neck and thorax images are obtained. After iodine (^{123}I) image acquisition, 185 to 370 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 pertechnetate (^{99m}Tc) is used to visualize the parathyroid, 40-150 MBq of sodium pertechnetate(^{99m}Tc) are injected and neck and thorax images are acquired 30 minutes later. Then 185-370 MBq of technetium (^{99m}Tc) sestamibi are injected and a second acquisition of images is acquired 10 minutes later.

- Dual-phase study :

350-1000MBq of technetium (^{99m}Tc) sestamibi are injected. Early (10 min. postinjection) and delayed (1.5-2.5 h postinjection) high-count images are obtained.

In case of kidney failure, exposure to ionising radiation can be increased. This must be taken into account when calculating the activity to be administered.

In general, activity selection for patients with a decreased hepatic function should be cautious, usually starting at the low end of the dosing range.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

If hypersensitivity or anaphylactoid 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.

Proper hydration and frequent voiding during the first few hours after injection are necessary to reduce bladder irradiation.

In newborns, infants, children and adolescents, special attention should be paid to the effective dose per MBq which is higher than in an adult, see sections 4.2 and 11.

In myocardial scintigraphy investigations under stress conditions, the general contraindications and precautions associated with the induction of ergometric or pharmacological stress should be considered.

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 52% relative to histological diagnosis. A negative examination does not exclude breast cancer especially in such a small lesion.

Radiopharmaceutical agents should be used only by qualified personnel with the appropriate government authorisation for use and manipulation of radionuclides. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisation.

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 or therapeutic result.

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

Pregnancy, see section 4.6.

Warnings related to excipients:

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

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions have been described to date.
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 Pregnancy and lactation

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

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

Lactation
Before administering a radioactive medicinal product to a mother who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until after the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk.

If the administration of the radioactive medicinal product is considered necessary, breast feeding should be interrupted for 24 hours and the expressed feeds discarded.

Close contact with infants should be restricted during this period.

4.7 Effects on ability to drive and use machines

STAMICIS has no 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.

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: Allergic skin and mucosa reactions with exanthema (pruritus, urticaria, oedema), vasodilatation, local reactions at the injection site, hypoaesthesia and paraesthesia, flushing.
Very rare: Other hypersensitivity reactions have been described in predisposed patients.
Not known (cannot be estimated from the available data): Erythema multiforme.

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.

Other disorders
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As most diagnostic nuclear medicinal product investigations are done with low radiation doses of less than 20 mSv these adverse events are expected to occur with a low probability. The effective dose calculated with an average amount of activity of 2000 MBq (500 at rest and 1500 MBq at stress) for a 1-day-protocol is 16.3 mSv

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 defecation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : diagnostic radiopharmaceuticals, Technetium (^{99m}Tc) compounds, ATC code :V09GA01

Pharmacodynamic effects are not expected after administration of technetium (^{99m}Tc) sestamibi.

After reconstitution with sodium pertechnetate (^{99m} Tc) solution for injection, the following complex forms technetium (^{99m}Tc) sestamibi:

$(^{99m}Tc)\ (MIBI)_6^+$ Where : MIBI = 2-methoxyisobutylisonitrile

Technetium (^{99m}Tc) sestamibi, when administered in usual activities and by the usual way, has no pharmacodynamic effects detectable clinically.

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

<u>Cardiac imaging</u>
Technetium (^{99m}Tc) sestamibi binds to the mitochondrial membrane and an intact mitochondrial membrane potential is important for intracellular binding.
The uptake of technetium (^{99m}Tc) 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 extraction for technetium (^{99m} Tc) sestamibi averaged 0.38 +/- 0.09. Technetium (^{99m}Tc) sestamibi from the blood is rapidly distributed into the tissue. Five minutes after injection only about 8 percent of the injected activity is still in circulation.

Technetium (^{99m}Tc) 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 (^{99m}Tc) 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 (^{99m}Tc) sestamibi is a substrate of P-glycoprotein. A direct correlation between the P-glycoprotein expression and the elimination of technetium (^{99m}Tc) sestamibi from tumours has been established. The cellular over-expression of P-glycoprotein could result in false negative images of tumours, especially of tumours larger than 1 cm.

Parathyroid imaging
In adenoma of the parathyroid glands blood flow and the number of mitochondria are increased.
This fact may explain the elevated uptake and trapping of technetium (^{99m}Tc) sestamibi in parathyroid adenoma.
Localization of technetium (^{99m}Tc) sestamibi appears to be dependent on blood flow to the tissue, the concentration of technetium (^{99m}Tc) sestamibi presented to the tissue, and the size of the parathyroid adenoma.

5.2 Pharmacokinetic properties

Technetium (^{99m}Tc) sestamibi is a cationic complex which accumulates in the viable myocardial tissue proportional to the regional coronary blood flow.

Technetium (^{99m}Tc) sestamibi from the blood is rapidly distributed into the tissue: 5 minutes after injection only about 8% of the injected dose is still in circulation.

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. Animal experiments have shown that uptake is not dependent on the functional capability of the Sodium-potassium pump. Irreversibly damaged cells however do not take up technetium (^{99m}Tc) sestamibi. The myocardial extraction level is reduced by hypoxia.
The clearance of the myocardial fraction is minimal and the redistribution is insignificant during at least 4 hours after an induced ischaemia in the dog. Technetium (^{99m}Tc) sestamibi is rapidly distributed from the blood into the tissue: 5 minutes after injection only about 8% of the injected dose is still in circulation.

However some experimental and clinical studies indicated a redistribution in severely ischaemic areas. A potential influence on the diagnostic quality of the test has not been established.

Scinti-mammography
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 localizes 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
The major metabolic pathway for clearance of technetium (^{99m}Tc) sestamibi is the hepatobiliary system. Activity 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.

Half-Life
The biological myocardial T½ is approximately 7 hours at rest and stress. The effective T½ (which includes biological and physical half-lives) is approximately 3 hours.

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 $(MIBI)_4$ 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.

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.

In vitro at cytoxic concentrations, an increase in chromosome aberration was observed in the 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 have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous chloride dihydrate
Cysteine hydrochloride monohydrate
Sodium Citrate
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

Kit: 1 year
Labelled product: after reconstitution, store in a refrigerator (2-8°C) and use within 10 hours

6.4 Special precautions for storage

Keep the vial in the outer carton, in order to protect from light.
Do not store above 25°C

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

Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

6.5 Nature and contents of container

15 mL multidose glass vial, type I borosilicate glass sealed with a bromobutyl rubber stopper and an aluminium caps.

Pack size: 5 vials

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

CIS bio international
B.P.32
F-91192 Gif sur -Yvette Cedex

8. MARKETING AUTHORISATION NUMBER

Denmark:	MTn°02241
Finland:	Mtnr 25091
Ireland:	PA 677/18/1
Norway:	MT nr 08-5992
United Kingdom:	PL 11876/0019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

Denmark:	10/10/2008
Finland:	09/12/2008
Ireland:	12/12/2008
Norway:	31/03/2009
United Kingdom:	07/10/2008

10. DATE OF REVISION OF THE TEXT

03/2009

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 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 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 kidneys in the proportions 75% and 25% respectively.

Dose absorbed after injection of technetium (^{99m}Tc) sestamibi (resting subject)

Organ	**Dose absorbed per activity administered [mGy/MBq] (rest test)**				
	Adult	15-years	10-years	5-years	1-year
Adrenal glands	0.0075	0.0099	0.015	0.022	0.038
Bladder walls	0.011	0.014	0.019	0.023	0.041
Bone surface	0.0082	0.010	0.016	0.021	0.038
Brain	0.0052	0.0071	0.011	0.016	0.027
Breasts	0.0038	0.0053	0.0071	0.011	0.020
Gall bladder	0.039	0.045	0.058	0.10	0.32
Alimentary 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	0.17
LLI	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	0.015
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
Bone 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
Testicles	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
Other 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

Doses absorbed after injection of technetium(^{99m} Tc) sestamibi (Exercise)

Organ	Dose absorbed per activity administered [mGy/MBq] (exercise test)				
	Adult	15-years	10-years	5-years	1-year
Adrenal glands	0.0066	0.0087	0.013	0.019	0.033
Bladder walls	0.0098	0.013	0.017	0.021	0.038
Bone surface	0.0078	0.0097	0.014	0.020	0.036
Brain	0.0044	0.0060	0.0093	0.014	0.023
Breasts	0.0034	0.0047	0.0062	0.0097	0.018
Gall bladder	0.033	0.038	0.049	0.086	0.26
Alimentary 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
ULI	0.022	0.028	0.046	0.072	0.13
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	0.11
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
Bone 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
Testicles	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
Other 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 dose calculated with an average amount of activity of 1800 MBq (900 MBq at stress and 900 MBq at rest) for a 2-day-protocol is 15.2mSv.
The effective dose calculated with an average amount of activity of 2000 MBq (500 MBq at rest and 1500 MBq at stress) for a 1-day-protocol is 16.3 mSv.

Evaluation of ventricular function
After injection of 800 MBq, the effective dose is 7.2 mSv at rest . After injection of 800 MBq, the effective dose is 6.3 mSv at stress.

Scinti-mammography
After injection of 1000 MBq, the effective dose is 9.0 mSv.

Parathyroid imaging of hyperfunctioning tissue
The effective dose after administration of 1000 MBq is 9.0 mSv.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Reconstitute with Sodium Pertechnetate (^{99m}Tc) Injection, Ph. Eur.

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.

This product contains no bacteriostatic preservative.

The freeze-dried product is packaged under nitrogen atmosphere.

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

Preparation of technetium (^{99m}Tc) sestamibi from the kit is to be done according to the following procedure, in compliance with aseptic and radioprotection rules:

A. Boiling procedure

1 Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the vial and disinfect the surface of the vial closure.

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 approximately 1 to 3 mL of the sterile, non-pyrogenic Sodium Pertechnetate (^{99m}Tc) solution (200 MBq to 11 GBq) .

4 Aseptically add the Sodium Pertechnetate (^{99m}Tc) 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 upside-down motions**.**

6 Remove the vial from the lead shield and place it **upright** in an appropriate boiling water bath, such that the vial is not directly in contact with the bottom of the bath, and keep boiling for 10 minutes. The bath must be shielded. Timing for the 10 minutes starts 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 and allow to cool for 15 minutes.

8 Inspect visually the vial content for the absence of particulate matter and discoloration prior to administration.

9 Aseptically withdraw technetium (^{99m}Tc) sestamibi using a sterile shielded syringe. Use within 10 hours of preparation.

10 Radiochemical purity should be checked prior to patient administration according to the radio TLC method as detailed below.

B. Heating block procedure

1 Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the Kit vial and disinfect the surface of the vial closure.

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 approximately 1 to 3 mL of the sterile, non-pyrogenic Sodium Pertechnetate (^{99m}Tc) solution (200 MBq to 11.1 GBq).

4 Aseptically add the Sodium Pertechnetate (^{99m}Tc) 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 upside-down motions.

6 Place the vial in the heating block previously heated to 100°C, and incubates for 15 min. The heating block should be adapted to the size of the vial in order to ensure a correct transfer of heat from the heating device to the content of the vial.

7 Remove the vial from the heating block and allow to cool for 15 minutes.

8 Inspect visually the vial content for the absence of particulate matter and discoloration prior to administration.

9 Aseptically withdraw technetium (^{99m}Tc) sestamibi using a sterile shielded syringe. Use within 10 hours of preparation.

10 Radiochemical purity should be checked prior to patient administration according to the Radio TLC Method as detailed below.

Quality Control of the Radiochemical Purity

Method

Thin Layer Chromatography

Materials

1 Aluminium Oxide plate, J.T. Baker « Baker-flex » IB-FTLC , pre-cut to 2.5 cm x 7.5 cm.

2 Ethanol 768 g/L

3 Activimeter for measuring radioactivity in the 0.7 – 12 GBq range.

4 1 mL syringe with a 22-26 gauge needle.

5 Small developing tank with cover, (100 mL beaker covered with plastic film is sufficient).

Procedure

1 Pour enough ethanol into the developing tank (beaker) to have a depth of 3-4 mm of solvent. Cover the tank (beaker) with plastic film and allow it to equilibrate for approximately 10 minutes.

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.

3 Apply 1 drop of the kit solution on top of the ethanol spot. Let the spot dry. **Do not heat.**

4 Develop the plate until the solvent rises to a distance of 5.0 cm from the spot.

5 Cut the strip 4.0 cm from the bottom, and measure the count rate of each piece in the activimeter.

6 Calculate the % Radiochemical purity as:

$$\% \text{ technetium } (^{99m}\text{Tc}) \text{ sestamibi} = \frac{(\text{Activity top portion})}{(\text{Total Activity})} \times 100$$

The radiochemical purity should be more than or equal to 94 %, otherwise the preparation should be discarded.

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