AUSTRALIAN PRODUCT INFORMATION – STAMICIS KIT FOR THE PREPARATION OF TECHNETIUM [99MTC] SESTAMIBI INJECTION VIAL [TETRAKIS(2-METHOXYISOBUTYLISONITRILE) COPPER (I) TETRAFLUOROBORATE] INTRAVENOUS INJECTION POWDER

1 NAME OF THE MEDICINE

Tetrakis (2-methoxyisobutyl isonitrile) copper (I)] tetrafluoroborate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg [Tetrakis (2-methoxyisobutyl isonitrile) copper (I)] tetrafluoroborate.
The radionuclide is not part of the kit.
For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

White powder for the preparation of technetium (^{99m}Tc) sestamibi intravenous injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

a) Technetium (^{99m}Tc) Sestamibi is indicated for use in conjunction with stress testing as an adjunct in the diagnosis of ischemic heart disease. In these patients additional information about ventricular function may be derived by using the first pass technique.
b) Technetium (^{99m}Tc) Sestamibi is indicated as a second line diagnostic aid to assist in the evaluation of patients for whom mammography is inconclusive.

4.2 DOSE AND METHOD OF ADMINISTRATION

<u>Dosimetry</u>

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 62 and are calculated according to the following assumptions: After intravenous injection the substance is rapidly cleared from the blood and taken up predominantly 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. The radiation doses to organs and tissues of an average patient (70 Kg) per MBq of Technetium [^{99m}Tc] Sestamibi injected intravenously are shown in the tables below. The effective dose resulting from an administered amount of 925 MBq in the adult is 7.9 mSv at rest and 6.9 mSv at stress.

Table 1. Radiation Dose to Patients from Radiopharmaceuticals Technetium [^{99m}Tc] Sestamibi (Resting Subject)
^{99m}Tc 6h

Organ	Adult
Adrenals	7.5E-03
Bladder	1.1E-02
Bone Surfaces	8.2E-03
Brain	5.2E-03
Breast	3.8E-03
Gall Bladder	3.9E-02
GI Tract	
Stomach	6.5E-03
SI	1.5E-02
ULI	2.7E-02
LLI	1.9E-02
Heart	6.3E-03
Kidneys	3.6E-02
Liver	1.1E-02
Lungs	4.6E-03
Muscles	2.9E-03
Oesophagus	4.1E-03
Ovaries	9.1E-03
Pancreas	7.7E-03
Salivary glands	1.4E-02
Red Marrow	5.5E-03
Skin	3.1E-03
Spleen	6.5E-03
Testes	3.8E-03
Thymus	4.1E-03
Thyroid	5.3E-03
Uterus	7.8E-03
Remaining organs	3.1E-03
Effective dose [mSv/MBq]	8.5E-03

(International Commission on Radiological Protection; ICRP Publication 62; November 1992)

Table 1. Radiation Dose to Patients from Radiopharmaceuticals Technetium [^{99m}Tc] Sestamibi (Resting Subject) ^{99m}Tc 6h	
Organ	**Adult**
Adrenals Bladder Bone Surfaces Brain Breast Gall Bladder	6.6E-03 9.8E-03 7.8E-03 4.4E-03 3.4E-03 3.3E-02
GI Tract Stomach SI ULI LLI	 5.9E-03 1.2E-02 2.2E-02 1.6E-02
Heart Kidneys Liver Lungs Muscles	7.2E-03 2.6E-02 9.2E-03 4.4E-03 3.2E-03
Oesophagus Ovaries Pancreas Salivary glands Red Marrow Skin	4.0E-03 8.1E-03 6.9E-03 5.0E-02 9.2E-03 2.9E-03
Spleen Testes Thymus Thyroid Uterus	5.8E-03 3.7E-03 4.0E-03 4.4E-03 7.2E-03
Remaining organs	3.3E-03
Effective dose [mSv/MBq]	7.5E-03

(International Commission on Radiological Protection; ICRP Publication 62; November 1992)

Cardiac imaging

The suggested dose range for I.V. administration to be employed in the average patient (70 Kg) is:

370-1110 MBq

For diagnosis of ischemic heart disease, two injections (exercise and rest) are required in order to differentiate transiently from persistently reduced myocardial uptake. After the injection, exercise if used should be encouraged for an additional one to two minutes. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration.

Image acquisition:
If possible, the patient should fast for at least four hours prior to the study and should have a light meal after injection to assist upper intestinal clearance of the tracer.

The heart to background ratio will increase with time but the ideal imaging time, reflecting the best compromise between heart count rate and contrast, is approximately 1-2 hours after a rest injection and 0.25-2 hours after a stress injection. There is no evidence for significant changes in myocardial tracer concentration, or redistribution, therefore imaging up to six hours post injection is possible.

Planar or tomographic imaging (both of which can be performed with ECG gating) can be used for diagnosis of ischemic heart disease. For planar imaging, the standard three view (anterior, 45° LAO; 70° LAO, or LL) planar projections should be used. Static imaging time should be sufficient to acquire at least 1 million counts per view (approximately 5 minutes/view). For gated acquisition, imaging time should be 8-10 minutes/view.
For tomographic imaging, acquisition time/projection should be approximately 30 seconds.

b) Dose for Breast imaging (Scintimammography):
The suggested dose range for Intravenous administration to be employed in the average patient (70 Kg) is **740 – 1110 MBq (20-30 mCi)**. The injection should be followed with a 10 mL saline flush

Image Acquisition:
It is generally suggested that images are obtained with a table overlay to separate breast tissue from the myocardium and liver, and to exclude potential activity that may be present in the opposite breast. For lateral images, position the patient prone with the isolateral arm comfortably above the head, shoulders flat against the table, head turned to the side and relaxed, with the breast imaged pendent through an overlay cutout. The breast should not be compressed on the overlay. For anterior images, position the patient supine with both arms behind the head. For either lateral or anterior images, shield the chest and abdominal organs, or remove them from the field of view.

For complete study, sets of images should be obtained five to ten minutes after the injection, and in the following sequence:

Beginning five to ten minutes after the injection of Technetium [^{99m}Tc] Sestamibi:
• ten-minute lateral image of breast with abnormality
• ten-minute lateral image of contralateral breast
• ten-minute anterior image of both breasts

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

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:

Method of preparation

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 additive-free, sterile, non-pyrogenic Sodium Pertechnetate (^{99m}Tc) solution (925 MBq to 5550 MBq).

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

7. Remove the vial from the water bath, place in the lead shield and allow to cool for fifteen minutes.

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

9. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium 99m concentration, total volume, assay time and date, expiration time and lot number on the vial shield label and affix the label to the shield.

10. Store the reaction vial containing technetium (^{99m}Tc) sestamibi below 25°C until use; at such time the product should be aseptically withdrawn. Technetium [^{99m}Tc] Sestamibi should be used within ten hours of preparation

Note: If repeated withdrawals are made, the replacement of the contents of the vial with air should be minimized, and separate syringes must be used for each patient.

11. Radiochemical purity should be checked prior to
patient administration according to the radio Thin-Layer Chromatography (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.

Note: If repeated withdrawals are made, the replacement of the contents of the vial with air should be minimized, and separate syringes must be used for each patient.

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

DETERMINATION OF RADIOCHEMICAL PURITY IN TECHNETIUM [^{99m}TC] SESTAMIBI

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 95%

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 2 drops of the kit solution, side by side 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.

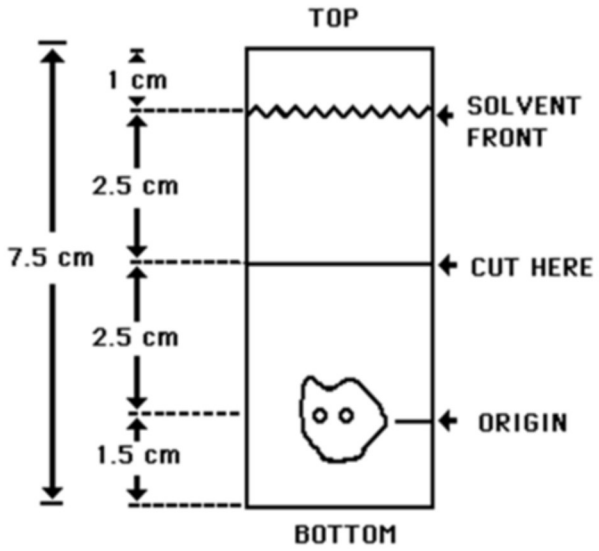
5 Cut the strip 4.0 cm from the bottom, and measure the count rate of each piece in the activimeter.

6 Calculate the % Radiochemical purity as:

% technetium (^{99m}Tc) sestamibi =

$$\frac{\text{(MBq Top piece)}}{\text{(MBq Both pieces)}} \times 100$$

TLC Plate Diagram



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

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

Dosage

Adults 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.

Paediatric population

Safety and effectiveness in subjects below the age of 18 have not been established.

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 4.2 DOSE AND METHOD OF ADMINISTRATION.

For patient preparation, see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

4.3 CONTRAINDICATIONS

There are no known contraindications.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 local competent authority.

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.

The technetium-99m labelling reactions depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate [^{99m}Tc] Injection containing oxidants should not be used.

The suitability of 99mTc-Pertechnetate derived from non-chromatographic generators has not been established for this product.

For instructions on extemporary preparation of the medicinal product before administration, see section 4.2 DOSE AND METHOD OF ADMINISTRATION. 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 minimize 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 person 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.

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

No data available.

Patient preparation

To minimize the radiation dose to the bladder and other organs the patient should increase fluid intake (unless medically contraindicated) and void as frequently as possible after the injection for up to six hours.

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 breast imaging (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

Patients in whom cardiac disease is known or suspected should be studied under medical supervision. Care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure. Infrequently, death has occurred 4 to 24 hours after technetium (99mTc) Sestamibi use and is usually associated with exercise stress testing.

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 SPECIAL PRECAUTIONS FOR DISPOSAL.

Use in the elderly

No data available.

Paediatric use

Safety and effectiveness in subjects below the age of 18 have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No date available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies on fertility have been performed.

Use in pregnancy – Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium [^{99m}Tc] Sestamibi. It is also not known whether Technetium [^{99m}Tc] Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium [^{99m}Tc] Sestamibi should not be given to a pregnant woman unless in the judgement of the treating clinician, its use is essential for the patient's welfare and the expected benefits outweigh the potential hazards.

Use in lactation

99mTc-Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium [^{99m}Tc] Sestamibi is excreted in human milk. Therefore, formula feedings should be substituted for breast feedings for at least 24 hours.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events were evaluated in 3741 adults who were evaluated in clinical studies. Of these patients, 3068 (77% men, 22% women, and 0.7% of the patients' genders were not recorded) were in cardiac clinical trials and 673 (100% women) in breast imaging trials. Cases of angina, chest pain, and death have occurred in cardiac imaging studies. Adverse events reported at a rate of 0.5% or greater after Technetium [^{99m}Tc] Sestamibi administration are shown in the following table:

Table 3: Selected Adverse Events Reported in >0.5% of Patients Who Received Technetium [99mTc] Sestamibi in Either Breast Or Cardiac Clinical Studies*

Body System	Breast Studies	Cardiac Studies		
	Women n = 673	Women n = 685	Men n = 2361	Total n = 3046
Headache	11 (1.6%)	2 (0.3%)	4 (0.2%)	6 (0.2%)
Nausea	4 (0.6%)	1 (0.1%)	2 (0.1%)	3 (0.1%)
Taste Perversion	129 (19.2%)	60 (8.8%)	157 (6.6%)	217 (7.1%)
Parosmia	8 (1.2%)	6 (0.9%)	10 (0.4%)	16 (0.5%)

*Excludes the 22 patients whose gender was not recorded.

In the clinical studies for breast imaging, breast pain was reported in 12 (1.7%) of the patients. In 11 of these patients the pain appears to be associated with biopsy/surgical procedures.

The following adverse reactions have been reported in ≤ 0.5% of patients: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis, angioedema, arrythmia, dizziness, syncope, vomiting, abdominal pain, pruritis, rash, urticaria, and severe hypersensitivity characterized by dyspnoea, hypotension, bradycardia, asthenia, and vomiting within two hours after a second injection of Technetium [^{99m}Tc] Sestamibi. A few cases of flushing, oedema, injection site inflammation, dry mouth, fever, and fatigue have also been attributed to administration of the agent.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Clinical trials

Breast Imaging:

Two multicenter trials enrolled 563 evaluable female subjects who were scheduled for excisional biopsy. In one trial the subjects had palpable breast abnormalities and in the other trial the subjects had mammographically-detected, non-palpable breast abnormalities. The mean age of the populations was 49.4 ± 13.2 years and 54.3 ± 11.7 years, respectively. In both trials about 70% of the population was Caucasian and approximately 15% each African-American and Hispanic.

Diagnostic evaluation included breast physical examination, mammography, scintigraphy and histopathology. For scintigraphy, lateral (10 minute) and anterior (10 minute) planar images were obtained beginning at 10 minutes after injection of 20-30 mCi of Technetium [^{99m}Tc] Sestamibi. Each scintigraphic image was read by the institutional physician who could have access to the patient's medical history and records of physical and mammographic findings and by three blinded readers who did not.

The table below describes the diagnostic statistics for scintigraphic imaging and mammography when compared to core laboratory histopathology are displayed below for subjects with palpable abnormalities:

Diagnostic Statistic, %	Institutional Scintigraphy Results (N=251)	Blinded Read Scintigraphy Results (N=205)	Institutional Mammography Results (N=262)	Core Mammography Results (N=246)
Sensitivity	95	82	95	94
Specificity	72	79	44	33
PPV	77	81	61	57
NPV	94	81	89	86
Agreement	83	81	68	63
Prevalence	49	51	49	48

The diagnostic statistics for scintigraphic imaging when compared to core laboratory histopathology are displayed below for subjects with mammographically-detected, non-palpable breast abnormalities:

Diagnostic Statistic, %	Institutional Scintigraphy Results (N=282)	Blinded Read Scintigraphy Results (N=271)	Institutional Mammography Results (N=320)	Core Mammography Results (N=307)
Sensitivity	72	55	-	-
Specificity	84	91	-	-
PPV	66	73	33	37
NPV	87	81	-	-
Agreement	80	79	-	-
Prevalence	31	31	-	-

PPV=Positive predictive value; NPV=Negative predictive value
Median findings are presented for blinded read results
Interreader agreement for the blinded read ranged from 95-100%

Across the two trials, diagnostic accuracy was similar for patients of differing likelihood of malignancy as assessed by a mammographer and for differing breast densities.

5.2 PHARMACOKINETIC PROPERTIES

99mTc Sestamibi is a cationic 99mTc complex which has been found to accumulate in myocardial tissue in proportion to regional bloodflow, analogous to Thallous [^{201}Tl] Chloride. Unlike Thallous [^{201}Tl] Chloride (which redistributes rapidly after the initial myocardial uptake), 99mTc Sestamibi does not undergo appreciable redistribution after the initial myocardial uptake. Therefore, separate stress and resting studies are required to differentiate between transiently and persistently reduced myocardial uptake. Animal cross-over experiments using Thallous [^{201}Tl] Chloride and 99mTc Sestamibi have confirmed that the myocardial distribution of 99mTc Sestamibi correlates well with regional myocardial perfusion.

Scintigraphic images obtained in animals and man after the intravenous administration of 99mTc Sestamibi have been comparable to those obtained with Thallous [^{201}Tl] Chloride in patients with coronary insufficiency.

Studies using subcellular fractionation and electron micrographic analysis of heart cell aggregates have shown that 99mTc Sestamibi cellular retention occurs specifically within the mitochondria as a result of electrostatic interactions. Secondary to increased metabolic requirements, cancer cells maintain more negative mitochondrial membrane potentials than normal cells. 99mTc Sestamibi uptake in cancer cells is thus a multifunctional process dependent on delivery to the tumor and retention by electrostatic interaction.

The major pathway for clearance of 99mTc Sestamibi is the hepatobiliary system. Twenty-seven percent of the injected dose is excreted in the urine, and approximately thirty-three percent of the injected dose is cleared through the faeces in 48 hours.

Blood clearance studies indicate that the fast clearing component clears with a t1/2 of 3.0 minutes at rest, and 2.0 minutes under exercise conditions. At five minutes post rest injection, 9.1% of the injected dose remains in circulation; at 5 minutes post stress injection 6.5%. The myocardial t1/2 is 9.8 hours (95% CI: 6.3 - 13.3 hours) after rest injection and 9.7 hours (95% CI: 3.8 - 15.7 hours) after a stress injection. The t1/2 for the liver is 33.1 minutes (95% CI: 20.2 - 45.9 minutes) after a rest injection and 47.0 minutes (95% CI: 20.6 - 73.5 minutes) after a stress injection. The ideal imaging time see section 4.2 DOSE AND METHOD OF ADMINISTRATION) reflects the best compromise between heart count rate and surrounding organ uptake.

Myocardial uptake is 1.5% (95% CI: 1.2 - 1.8%) of the injected dose at exercise and 1.2% (95% CI: 0.8 - 1.6%) at rest. Animal studies have shown that uptake is coronary flow dependent and not blocked when the sodium pump mechanism is inhibited. However, hypoxia reduces the level of myocardial extraction.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Several mutagenicity studies indicate that $[Cu(MIBI)_4]BF_4$ is not likely to induce mutagenic changes. However, in an in vitro study on human lymphocytes, $[Cu(MIBI)_4]BF_4$ resulted in chromosomal aberrations.

Carcinogenicity

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
Cysteine hydrochloride monohydrate
Sodium Citrate
Mannitol

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

The information on the shelf life of Stamicis Kit for the preparation of technetium [^{99m}Tc] sestamibi injection vial [tetrakis(2-methoxyisobutylisonitrile) copper (I) tetrafluoroborate] Intravenous injection powder can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After reconstitution and radiolabelling, store below 25°C and use within 10 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep the vials in the outer carton, in order to protect from light.

For storage conditions of the reconstituted after radiolabelling of the medicinal product, see section 6.3 SHELF LIFE. Storage of radiopharmaceuticals should be in accordance with national regulation 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 x 15 mL vials and 5 x radiolabelling labels

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

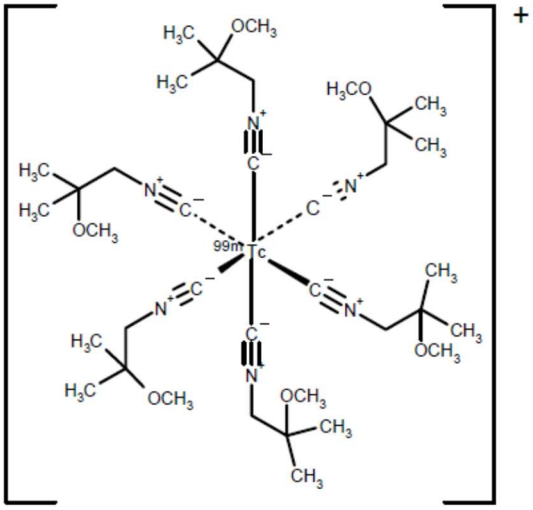
In Australia, any unused medicine or radioactive waste material should be disposed off in accordance with Code for the disposal of radioactive wastes by the userwhich is published on the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) website as Radiation Protection Series (RPS C-6).

6.7 PHYSICOCHEMICAL 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

Chemical structure:



Chemical Formula: $C_{36}H_{66}N_6O_6Tc$

CAS number: 109581-73-9

PHYSICAL CHARACTERISTICS

Technetium ^{99m}Tc decays by isomeric transition with a physical half-life of 6 hours. Photons associated with this transition which are useful for detection and imaging studies are listed below:

Table 4. Principal Radiation Emission Data		
Principal Radiation	Mean% / Disintegration	Mean Energy (keV)
Gamma-2	87.2	140.5

Reference: Browne E., Firestone R.B., and Shirley V.S., (Ed.) Table of Radioactive Isotopes, 1986, J. Wiley

Table 5. Physical Decay Chart; ^{99m}Tc Half-Life 6 Hours			
Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	8	.397
1	.891	9	.354
2	.794	10	.315
3	.707	11	.281
4	.630	12	.250
5	.561		
6	.500		
7	.445		

*Calibration Time

EXTERNAL RADIATION

The specific gamma ray constant for ^{99m}Tc is 0.19 mGy per MBq-h at 1cm. The first half value thickness of lead (Pb) for ^{99m}Tc is 0.2 mm. Attenuation by lead is given in the following Table:

Table 6. Radiation Attenuation by Lead Shielding	
Shield Thickness (Pb) mm	Coefficient of Attenuation
0.95	0.1
1.8	0.01
2.7	0.001
3.6	0.0001

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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9 DATE OF FIRST APPROVAL

18/02/2026

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information