AUSTRALIAN PRODUCT INFORMATION

TECHNESCAN® SESTAMIBI

(tetrakis (2-methoxyisobutylisonitrile) copper(1) tetrafluoroborate)

1 NAME OF THE MEDICINE

Tetrakis (2-methoxyisobutylisonitrile) copper (I) tetrafluoroborate.

The abbreviated notation is $[Cu(MIBI)_4]BF_4$ (where MIBI is 2-methoxyisobutylisonitrile).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TECHNESCAN® SESTAMIBI is a kit for radiopharmaceutical preparation of Technetium [^{99m}Tc] Sestamibi Injection. Each vial contains 1 mg of tetrakis (2-methoxyisobutylisonitrile) copper (I) tetrafluoroborate.

TECHNESCAN® SESTAMIBI is a sterile, nonpyrogenic, lyophilised white powder. After reconstitution of the radiopharmaceutical kit with sterile, non-pyrogenic, oxidant free Sodium Pertechnetate (^{99m}Tc) Injection, the solution for injection is clear and colourless and a complex of the MIBI and Technetium-99m forms yielding Technetium [^{99m}Tc] Sestamibi ([Tc-99m $(MIBI)_6]^+Cl^-$).
The pH of the reconstituted product is 5.5 (5.0 to 6.0). No bacteriostatic preservative is present. The contents of the vial are stored under nitrogen.

For the full list of excipients, see section 6.1 List of Excipients

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 in Table 1.

Table 1. Principal Radiation Emission Data[1]

Principal Radiation M	Mean %/Disintegration	Mean Energy (keV)
Gamma-2	87.2	140.5

[1] Browne E., Firestone R.B., and Shirley V.S., (Ed.) Table of Radioactive Isotopes, 1986, J. Wiley
keV=Kilo Electron Volt

Table 2. Physical Decay Chart; ^{99m}Tc Half-Life 6 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.445
1	0.891	8	0.397
2	0.794	9	0.354
3	0.707	10	0.315
4	0.630	11	0.281
5	0.561	12	0.250
6	0.500		

**Calibration time*

External Radiation

The specific gamma ray constant for ^{99m}Tc is 0.19 milligray (mGy) per MBq-h at 1 cm. The first half value thickness of lead (Pb) for ^{99m}Tc is 0.2 mm. Attenuation by lead is given in Table 3.

Table 3. 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

3 PHARMACEUTICAL FORM

Powder for Injection.

TECHNESCAN® SESTAMIBI is a white to almost white lyophilised powder or pellets in a glass vial for intravenous injection. To be reconstituted with sodium pertechnetate (^{99m}Tc) solution for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TECHNESCAN® SESTAMIBI is indicated for use in conjunction with stress testing as an adjunct in the diagnosis of ischaemic heart disease. In these patients additional information about ventricular function may be derived by using the first pass technique.

TECHNESCAN® 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

Dosage

Cardiac Imaging

The suggested dose range for intravenous administration to be employed in the average patient (70 kg) is: 370 to 1110 megabecquerel (MBq).

For diagnosis of ischaemic 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 been encouraged for an additional one to two (1 to 2) minutes.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration.

Radiochemical purity should be checked prior to patient administration.

Parenteral injection products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. **Adequate radiation shielding should be used for the inspection**.

Breast Imaging

The suggested dose range for intravenous administration to be employed in the average patient (70 kg) is 740 to 1110 MBq (20 to 30 millicurie [mCi]). The injection should be followed with a 10 mL saline flush.

Method of Administration

Imaging Acquisition

Cardiac Imaging

If possible, the patient should fast for at least four (4) 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 to 2 hours after a rest injection and 0.25 to 2 hours after a stress injection. There is no evidence of significant changes in myocardial tracer concentration, or redistribution, therefore imaging up to six (6) hours post injection is possible. Planar or tomographic imaging (both of which can be performed with ECG gating) can be used for diagnosis of ischaemic 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.

Breast Imaging

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 cut out. 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 (5 to 10) minutes after the injection of Technetium [^{99m}Tc] Sestamibi:

- Ten (10) minute lateral image of breast with abnormality
- Ten (10) minute lateral image of contralateral breast
- Ten (10) minute anterior image of both breasts.

Instructions for Preparation of Technetium [99mtc] Sestamibi for Injection

Preparation of the Technetium [^{99m}Tc] Sestamibi Injection from TECHNESCAN® SESTAMIBI Kit for the Preparation of Technetium [^{99m}Tc] Sestamibi is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate [^{99m}Tc] Injection to the vial, inspect the vial carefully for the presence of damage, particularly cracks, and do not use the vial if found.

b. Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the vial and swab the top of the vial closure with alcohol to sanitise the surface.

c. Place the vial in a suitable radiation shield with a fitted radiation cap.

d. With a sterile shielded syringe, aseptically obtain additive free, sterile, non-pyrogenic Sodium Pertechnetate [^{99m}Tc] Injection (925 to 5550 MBq, (25 to 150 mCi)) in approximately 1 to 3 mL.

e. Aseptically add the Sodium Pertechnetate [^{99m}Tc] Injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.

f. Shake vigorously, about 5 to 10 quick upward-downward motions.

g. Remove the vial from the lead shield and place upright in an appropriately shielded and contained boiling water bath, such that the vial is suspended above the bottom of the bath, and boil for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again. Do not allow the boiling water to come in contact with the aluminium crimp.

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

h. Remove the vial from the water bath, place in the lead shield and allow to cool for fifteen (15) minutes.

i. Using proper shielding, the vial contents should be visually inspected. Use only if the solution is clear and free of particulate matter and discoloration.

j. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium (^{99m}Tc) concentration, total volume, assay time and date, expiration time and lot number on the radioassay information label provided and affix the label to the shield.

k. Store the reaction vial containing the Technetium [^{99m}Tc] Sestamibi below 25°C until use; at such time the product should be aseptically withdrawn. The vial contains no preservative. Technetium [^{99m}Tc] Sestamibi should be used within six (6) hours of preparation. The vial contains no preservative.

Note: Adherence to the above product reconstitution instructions is important.

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

Product should be used within 6 hours after preparation.

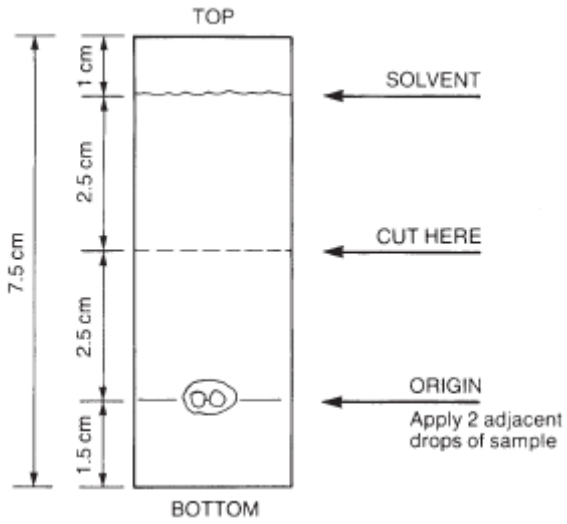
Final product with radiochemical purity of at least 90% was used in the clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method.

Determination of Radiochemical Purity in Technetium [99mTc] Sestamibi

1. Obtain a Baker-Flex Aluminium Oxide coated, plastic TLC plate, #1 B-F, pre-cut to 2.5 cm x 7.5 cm.
2. Dry the plate or plates at 100°C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.
3. Apply 1 drop of 95% ethanol*, 5% water using a 1 mL syringe with a 22 to 26 gauge needle, 1.5 cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY. *The ethanol used in this procedure should be 95% or greater.
4. Add 2 drops of Technetium [^{99m}Tc] Sestamibi solution, side by side on top of the ethanol spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).
5. Develop the plate in the covered TLC tank in ethanol for a distance of 5 cm from the point of application.
6. Cut the TLC plate 4 cm from the bottom and measure the ^{99m}Tc activity in each piece by appropriate radiation detector.
7. Calculate the % ^{99m}Tc Sestamibi as:

$$\% \ ^{99m}\text{Tc Sestamibi} = \frac{\text{MBq Top Piece}}{\text{MBq Both Pieces}} \times 100$$

8. Do not use if the ^{99m}Tc Sestamibi content is less than 90%.



Radiation Dosimetry

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 4 and 5. The effective dose resulting from an administered amount of 925 MBq in the adult is 8.3 millisievert (mSv) at rest and 7.3 mSv at stress.

Table 4. Radiation Dose to Patients from Radiopharmaceuticals Technetium [^{99m}Tc] Sestamibi (Exercise)

^{99m} Tc 6.02 h

	Absorbed Dose per unit activity administered (mGy/MBq)
Organ	**Adult**
Adrenals	6.6E-03
Bladder	9.8E-03
Bone Surfaces	7.8E-03
Brain	4.4E-03
Breast	3.4E-03
Gall Bladder	3.3E-02
GI Tract	
Stomach	5.9E-03
SI	1.2E-02
Colon	1.9E-02
ULI	2.2E-02
LLI	1.6E-02
Heart	7.2E-03
Kidneys	2.6E-02
Liver	9.2E-03
Lungs	4.4E-03
Muscles	3.2E-03
Oesophagus	4.0E-03
Ovaries	8.1E-03
Pancreas	6.9E-03
Red Marrow	5.0E-03
Salivary Glands	9.2E-03
Skin	2.9E-03
Spleen	5.8E-03
Testes	3.7E-03
Thymus	4.0E-03
Thyroid	4.4E-03
Uterus	7.2E-03
Remaining Organs	3.3E-03
Effective Dose (mSv/MBq)	7.9E-03

(International Commission on Radiological Protection, ICRP Publication 80; March 1998)

Table 5. Radiation Dose to Patients from Radiopharmaceuticals Technetium [^{99m}Tc] Sestamibi (Resting Subject)

^{99m}Tc 6.02 h

	Absorbed Dose per unit activity administered (mGy/MBq)
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
Colon	2.4E-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
Red Marrow	5.5E-03
Salivary Glands	1.4E-02
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)	9.0E-03

(International Commission on Radiological Protection, ICRP Publication 80; March 1998)

4.3 CONTRAINDICATIONS

Hypersensitivity to the active ingredient.

In myocardial scintigraphy investigations under stress conditions (i.e. exercise stress test), 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.

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 (4) hours prior to the examination. 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.

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 [^{99m}Tc] Sestamibi use and is usually associated with exercise stress testing.

The 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 components of the kit are sterile and non-pyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation.
The technetium-99m (^{99m}Tc) labeling reactions depend on maintaining the stannous ion in the reduced state, hence, Sodium Pertechnetate [^{99m}Tc] Injection containing oxidants should not be used.

Contents of the kit before preparation are not radioactive. However, after the Sodium Pertechnetate [^{99m}Tc] Injection is added, adequate shielding of the final preparation must be maintained.

Technetium [^{99m}Tc] Sestamibi, as well as other radioactive agents, must be handled with care and appropriate safety measures should be used to minimise radiation exposure to clinical personnel. Also, care should be taken to minimise radiation exposure to the patients consistent with proper patient management.

The suitability of pertechnetate (^{99m}Tc) derived from non-chromatographic generators has not been established for this product.

This product contains no antimicrobial preservative. It should be reconstituted aseptically and used within six (6) hours of reconstitution.

To minimise 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 (6) hours.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorised to license the use of radionuclides.

Use in hepatic impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Use in renal impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

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

Cardiac medications

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 medication should be taken into consideration when interpreting the results of the scintigraphic examination (ie exercise stress test). The recommendations of the applicable guidelines on ergometric or pharmacological stress tests should be followed.

Proton pump inhibitors

The use of proton pump inhibitors has shown to be significantly associated with gastric wall uptake. Its proximity to the inferior myocardial wall may lead to either false-negative or false-positive findings, and therefore to an inaccurate diagnosis. A withdrawal period for at least 3 days is recommended.

Iodine products

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 sodium iodide (^{123}I) or sodium pertechnetate (^{99m}Tc) product information documents.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been performed.

Use in 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 foetal 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 judgment of the treating clinician, its use is essential for the patient's welfare and the expected benefits outweigh the potential hazards.

Use in lactation

Pertechnetate (^{99m}Tc) 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

TECHNESCAN® SESTAMIBI has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

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 patient's 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 Table 6.

*Table 6: Selected Adverse Events Reported in >0.5% if patients who received Technetium [^{99m}Tc] 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%)
Parasomnia	8 (1.2%)	6 (0.9%)	10 (0.4%)	16 (0.5%)

*Excludes the 22 patients whose gender were 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, arrhythmia, 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.

Post-Marketing Experience

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 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, 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 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/reportingproblems.

4.9 OVERDOSAGE

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

This information is not available.

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 to30 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 diagnostic statistics for scintigraphic imaging and mammography when compared to core laboratory histopathology are displayed in Table 7 below for subjects with palpable abnormalities:

Table 7. Diagnostic Statistics Scintigraphic Imaging and Mammography (palpable abnormalities)

Diagnostic Statistic %	Institutional Scintigraphy Results	Blinded Read Scintigraphy Results	Institutional Mammography Results	Core Mammography Results
	(n=251)	(n=205)	(n=262)	(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

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

The diagnostic statistics for scintigraphic imaging when compared to core laboratory histopathology are displayed in Table 8 below for subjects with mammographically-detected, non-palpable breast abnormalities:

Table 8. Diagnostic Statistics for Scintigraphic Imaging (mammographically-detected, non palpable abnormalities)

Diagnostic Statistic %	Institutional Scintigraphy Results	Blinded Read Scintigraphy Results	Institutional Mammography Results	Mammography Results
	(n=282)	(n=271)	(n=320)	(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
Inter-reader 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

Distribution

Technetium [^{99m}Tc] Sestamibi is a cationic ^{99m}Tc complex which has been found to accumulate in myocardial tissue in proportion to regional blood flow, analogous to Thallous [^{201}Tl] Chloride. However, unlike Thallous [^{201}Tl] Chloride (which redistributes rapidly after the initial myocardial uptake), Technetium [^{99m}Tc] 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 Technetium [^{99m}Tc] Sestamibi have confirmed that the myocardial distribution of Technetium [^{99m}Tc] Sestamibi correlates well with regional myocardial perfusion.

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

Metabolism Studies using subcellular fractionation and electron micrographic analysis of heart cell aggregates have shown that Technetium [^{99m}Tc] 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. Technetium [^{99m}Tc] Sestamibi uptake in cancer cells is thus a multifunctional process dependent on delivery to the tumor and retention by electrostatic interaction.

Excretion

The major pathway for clearance of Technetium [^{99m}Tc] 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 $t_{1/2}$ of 3 minutes at rest, and 2 minutes under exercise conditions. At five (5) minutes post rest injection, 9.1% of the injected dose remains in circulation; at 5 minutes post stress injection 6.5%. The myocardial $t_{1/2}$ 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 $t_{1/2}$ for the liver is 33.1 minutes (95% CI: 20.2 - 45.9 minutes) after a rest injection and 47 minutes (95% CI: 20.6 - 73.5 minutes) after a stress injection. The ideal imaging time (See Section 4.2) 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

Genotoxicty

No data available.

Carcinogenicity

No long-term animal studies have been performed to evaluate carcinogenic potential or whether Technetium [^{99m}Tc] Sestamibi affects fertility in males or females. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cysteine hydrochloride monohydrate

Mannitol

Sodium citrate dihydrate

Stannous chloride dihydrate

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment).

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2 - Instructions for Preparation of Technetium [99mtc] Sestamibi for Injection.

6.3 SHELF-LIFE

Before reconstitution: 24 months

After reconstitution: Use within six (6) hours of preparation.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Before reconstitution: Store below 25^{o}C. Protect from light

After reconstitution: Store below 25^{o}C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mL glass vial.

Packs contain 5 vials.

Each 5 vial kit contains one pack insert and 5 radioassay information labels (to be attached to the shield).

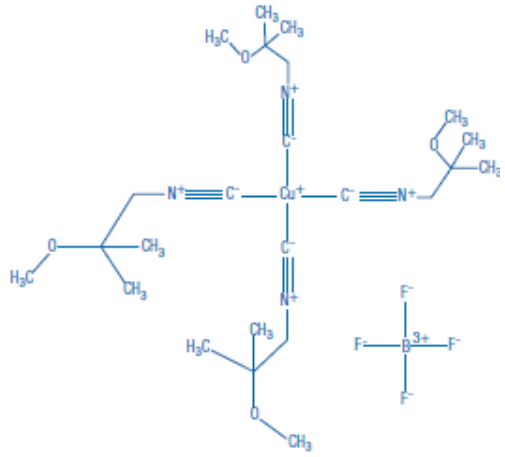
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The structural formula is:



The molecular formula is $C_{24}H_{44}N_4O_4BF_4Cu$ and the molecular weight is 602.98.

CAS number

The CAS number is 103694-84-4.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not considered for scheduling.

8 SPONSOR

Landauer Radiopharmaceuticals Pty Ltd

Level 3/69 Phillip Street

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Australia

9 DATE OF FIRST APPROVAL

8 September 2011.

10 DATE OF REVISION

14 September 2021.

Summary Table of Changes

Section changed	Summary of new information
All sections	Adopted new TGA approved PI form. New text added were necessary to comply with the TGA approved PI form.
4.3, 4.4, 4.5 and 4.8.	Text added for new safety information.