PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

KIT FOR THE PREPARATION OF TECHNETIUM Tc 99m SESTAMIBI INJECTION

Freeze-dried Powder for Solution, 1 mg/vial and Intravenous

Professed Standard

Radiodiagnostic Agent (Myocardial Imaging), V09GA0

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RECENT MAJOR LABEL CHANGES

Section 4: Dosage and Administration, 4.1: Dosing Considerations	06/2022
Section 9: Drug Interactions, 9.2: Drug Interactions Overview	06/2022
Section 9: Drug Interactions, 9.4: Drug-Drug Interactions	06/2022

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Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Kit for the preparation of Technetium Tc 99m Sestamibi Injection is indicated for:

- **Myocardial Imaging**: Technetium Tc 99m Sestamibi is useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction; and for the diagnosis and localization of ischaemic heart disease and coronary artery disease.
- Technetium Tc 99m Sestamibi is also useful in the assessment of global ventricular function by the first pass technique.

1.1 Pediatrics

Pediatric (below 18 years old): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatric: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

None known. However, patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container should advise their physician.

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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Refer to Section 7 WARNINGS AND PRECAUTIONS.

Interruption of proton pump inhibitor therapy for at least 3 days prior to the use of this product in cardiac imaging procedures is recommended.

4.2 Recommended Dose and Dosage Adjustment

The suggested dose range for I.V. administration to be employed in the average patient (70 kg) is: 370-1110 MBq (10 – 30 mCi). No dosage adjustment is required for patient with hepatic or renal impairment.

Health Canada has not authorized an indication for pediatric (below 18 years of age) or geriatric use.

4.3 Reconstitution

Parenteral Products:

The contents of the vial are intended only for use in the preparation of Technetium Tc 99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure. Store at 15°C to 25°C before and after reconstitution.

Remaining product or components should be disposed of in a safe manner, in compliance with applicable regulations. Refer to Section 11 STORAGE, STABILITY AND DISPOSAL.

Table 1: Reconstitution.

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
10 mL	25 – 150 mCi of Sodium pertechnetate Tc 99m in approximately 1 to 3 mL	1 to 3 mL	Ranging from 25 to 50 mCi/mL of Technetium Tc 99m Sestamibi

4.4 Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

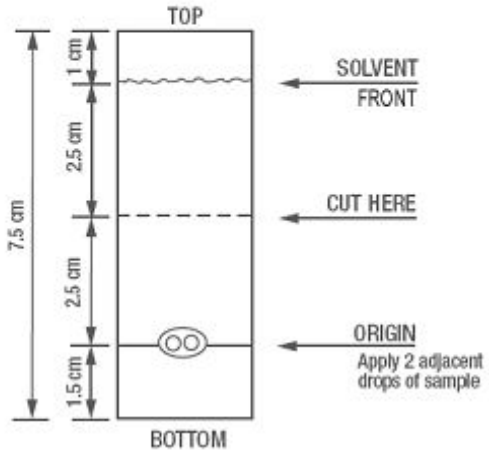
The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration. Radiochemical purity should be checked prior to patient administration. Do not use if radiochemical purity is less than 90%.

Determination of Radiochemical Purity in Technetium Tc 99m Sestamibi:

1. Obtain a Baker-Flex Aluminum 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 ethanol* using a 1-mL syringe with a 22–26 gauge needle, 1.5 cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY.
4. Add 2 drops of Technetium Tc 99m 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. The TLC tank is prepared by pouring ethanol* to a depth of 3–4 mm. Cover the tank and let it equilibrate for ~10 minutes.
6. Develop the plate in the covered TLC tank in ethanol* for a distance of 5 cm from the point of application.
7. Cut the TLC plate 4 cm from the bottom and measure the Tc 99m activity in each piece by appropriate radiation detector.
8. Calculate the % Tc 99m Sestamibi as:

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

TLC Plate Diagram



9. The dose should contain Tc 99m Sestamibi ≥ 90%. Do not use if radiochemical purity is less than 90%.

* The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99%) should remain at ≥95% ethanol content for one week after opening if stored tightly capped, in a cool dry place.

4.5 Missed Dose

Not applicable.

4.6 Image Acquisition and Interpretation

No data available.

4.7 Instructions for Preparation and Use

Preparation of the Technetium Tc 99m Sestamibi from the Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc 99m Injection to the vial, inspect the vial carefully for the presence of damage, particularly cracks, and do not use the vial if found. Tear off a radiation symbol and attach it to the neck of the vial.

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 sanitize 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 Tc 99m Injection [925–5550 MBq, (25–150 mCi)] in approximately 1 to 3 mL.

e. Aseptically add the Sodium Pertechnetate Tc 99m 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 aluminum crimp.

h. Remove the vial from the water bath, place in the lead shield and allow to cool for 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 Tc 99m concentration, total volume, assay time and date, expiration time and lot number on the radioassay information label and affix the label to the shield.

k. Store the reaction vial containing the Technetium Tc 99m Sestamibi at 15°C to 25°C until use; at such time the product should be aseptically withdrawn. Technetium Tc 99m Sestamibi should be used within 6 hours of preparation. The vial contains no preservative.

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

Curium Canada Inc.'s Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is not to be used with the Recon-o-Stat™ thermal cycler due to the smaller vial size requirements of this heating device.

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

4.8 Radiation Dosimetry

Estimates of radiation doses to organs and tissues of an average patient (70 Kg) per 1110 MBq (30 mCi) of Technetium Tc 99m Sestamibi injected intravenously are shown below in **Tables 2 and 3**.

Table 2: Radiation Absorbed Doses From Tc 99m Sestamibi at Rest (Stabin, M., July, 1990, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831).

ORGAN	rad/30 mCi	mGy/1110 MBq	rad/30 mCi	mGy/1110 MBq
	REST			
	2.0 hour void		4.8 hour void	
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Lower Large intestine Wall	3.9	40.0	4.2	41.1
Small Intestine	3.0	30.0	3.0	30.0
Stomach	0.6	6.1	0.6	5.8

ORGAN	rad/30 mCi	mGy/1110 MBq	rad/30 mCi	mGy/1110 MBq
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Heart Wall	0.5	5.1	0.5	4.9
Kidneys	2.0	20.0	2.0	20.0
Liver	0.6	5.8	0.6	5.7
Lungs	0.3	2.8	0.3	2.7
Ovaries	1.5	15.5	1.6	15.5
Red Marrow	0.5	5.1	0.5	5.0
Bone Surfaces	0.7	6.8	0.7	6.4
Testes	0.3	3.4	0.4	3.9
Thyroid	0.7	7.0	0.7	2.4
Urinary Bladder	2.0	20.0	4.2	41.1
Total Body	0.5	4.8	0.5	4.8
	rem/30 mCi	**mSv/1110 MBq**	**rem/30 mCi**	**mSv/1110 MBq**
Effective Dose Equivalent	1.5	15.5	1.7	16.7

Table 3: Radiation Absorbed Doses From Tc 99m Sestamibi Under Stress (Stabin, M., July, 1990, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831).

ORGAN	rad/30 mCi	mGy/1110 MBq	rad/30 mCi	mGy/1110 MBq
	STRESS			
	2.0 hour void		**4.8 hour void**	
Breasts	0.2	2.0	0.2	1.8
Gallbladder Wall	2.8	28.9	2.8	27.8
Lower Large intestine Wall	3.3	32.2	3.3	32.2
Small Intestine	2.4	24.4	2.4	24.4
Stomach	0.6	5.3	0.5	5.2
Upper Large Intestine Wall	4.5	44.4	4.5	44.4
Heart Wall	0.5	5.6	0.5	5.3
Kidneys	1.7	16.7	1.7	16.7
Liver	0.4	4.2	0.4	4.1
Lungs	0.3	2.6	0.2	2.4
Ovaries	1.2	12.2	1.3	13.3
Red Marrow	0.5	4.6	0.5	4.4
Bone Surfaces	0.6	6.2	0.6	6.0
Testes	0.3	3.1	0.3	3.4
Thyroid	0.3	2.7	0.2	2.4
Urinary Bladder	1.5	15.5	3.0	30.0
Total Body	0.4	4.2	0.4	4.2
	rem/30 mCi	**mSv/1110 MBq**	**rem/30 mCi**	**mSv/1110 MBq**
Effective Dose Equivalent	1.3	13.3	1.4	14.4

5 OVERDOSAGE

Clinical consequences of overdosage with Kit for the Preparation of Technetium Tc 99m Sestamibi Injection have not been reported.

In the event of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body using reinforced hydration and frequent bladder voiding. A diuretic might also be considered. If possible, an estimate of the radioactive dose given to the patient should be performed. For management of a suspected drug overdose, contact your regional poison control center.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is supplied as a 10-mL vial in a kit of five (5). Each 10-mL vial contains a sterile, non-pyrogenic, lyophilized mixture as described in the table below.

Table 4: Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Powder for solution, 1 mg/10-mL vial of Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate	• 1 mg L-cysteine hydrochloride monohydrate • 20 mg mannitol • 2.6 mg sodium citrate dihydrate • 0.075 mg stannous chloride, dihydrate ($SnCl_2 \bullet 2H_2O$) • 0.025 mg stannous chloride, dihydrate minimum ($SnCl_2 \bullet 2H_2O$) • 0.086 mg tin chloride (stannous and stannic) dihydrate, maximum (as $SnCl_2 \bullet 2H_2O$)

Prior to lyophilization the pH is between 5.6 – 5.7. The contents of the vial are lyophilized and stored under nitrogen. Protect from light prior to reconstitution. The Kit for the Preparation of Technetium Tc 99m Sestamibi Injection contains no preservatives.

Store at 15°C to 25°C before and after reconstitution.

Included in each five (5) vial kit is one (1) package insert and five (5) radioassay information labels.

6.1 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. Photons that are useful for detection and imaging studies are listed in **Table 5**.

Table 5: Principal Radiation Emission Data (Kocher, David C., Radioactive Decay Tables, DOE/TIC-11026, 108 (1981)).

Radiation	Mean % / Disintegration	Mean Energy (KeV)
Gamma-2	89.07	140.5

6.2 External Radiation

The specific gamma ray constant for Tc 99m is 5.4 microcoulombs/Kg-MBq-hr (0.78 R/mCi-hr) at 1 cm. The first half value layer is 0.017 cm of Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in **Table 6**. To facilitate control of the radiation exposure from Megabecquerel (millicurie) amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of 1,000.

Table 6: Radiation Attenuation by Lead Shielding.

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	0.1
0.16	0.01
0.25	0.001
0.33	0.0001

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in **Table 7**.

Table 7: Physical Decay Chart; Tc 99m Half-Life 6.02 Hours.

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

* Calibration Time

7 WARNINGS AND PRECAUTIONS

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

General

The contents of the vial are intended only for use in the preparation of Technetium Tc 99m Sestamibi Injection and are not to be administered directly to the patient without first undergoing the preparative procedure.

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

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.

Technetium Tc 99m labeling reactions depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc 99m Injection containing oxidants should not be used.

Technetium Tc 99m Sestamibi should not be used more than six hours after preparation.

Caution should be exercised, and emergency equipment should be available when administering Technetium Tc 99m Sestamibi. Also, before administering Technetium Tc 99m Sestamibi, patients should be asked about the possibility of allergic reactions to the drug.

Carcinogenesis and Mutagenesis

Refer to Section 16 NON-CLINICAL TOXICOLOGY.

In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.5 rads/30 mCi at rest, 1.2 rads/30 mCi at exercise) is high. Minimal exposure (ALARA) is necessary in women of childbearing capability (see **RADIATION DOSIMETRY** section).

Cardiovascular

In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure.

Contamination

The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product: toilet should be used instead of urinal; toilet should be flushed several times after use. If blood or urine gets onto clothing, such clothing should be washed separately or stored for 1 to 2 weeks to allow for decay.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

Monitoring and Laboratory Tests

Blood pressure, laboratory or other tests are required to monitor response to therapy and possible adverse reactions. Please refer to WARNINGS AND PRECAUTIONS section above.

Reproductive Health: Female and Male Potential

- **Fertility**

  Animal reproduction studies have not been conducted with Technetium Tc 99m Sestamibi. It is also not known whether Technetium Tc 99m Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

- **Teratogenic Risk**

  Animal teratogenicity studies have not been conducted with Technetium Tc 99m Sestamibi.

7.1 Special Populations

7.1.1 Pregnant Women

There have been no studies in pregnant women. Technetium Tc 99m Sestamibi should be given to a pregnant woman only if clearly needed. Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of women of childbearing capability, should be performed during the first ten days following the onset of menses, or after ensuring the woman is not pregnant. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

7.1.2 Breastfeeding

Technetium Tc 99m Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium Tc 99m Sestamibi is excreted in human milk. Therefore, formula feedings should be substituted for breastfeedings.

7.1.3 Pediatrics

Pediatric (below 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatric: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

An overview of selected adverse events is reported in **Table 8**. The most serious adverse reactions that have occurred are chest pain/angina, ST segment changes and death. These were reported in cardiac imaging clinical trials.

The most frequently occurring adverse reactions in all clinical trials were taste perversion, chest pain/angina and ST segment changes.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 receiving Technetium Tc 99m Sestamibi administration are shown in the following table:

Table 8: Selected Adverse Events Reported in > 0.5% of Patients Who Received Technetium Tc 99m 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%)
Chest Pain/Angina	0 (0%)	18 (2.6%)	46 (1.9%)	64 (2.1%)
ST Segment Changes	0 (0%)	11 (1.6%)	29 (1.2%)	40 (1.3%)
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 genders 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.

It should be noted that the above data on Adverse Events reported in breast studies is provided for safety information purposes only and that the Curium Sestamibi product is not indicated for breast imaging.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions have been reported in ≤ 0.5% of patients:

- Cardiac disorders: Arrhythmia;
- Gastrointestinal disorders: Abdominal pain, Dry mouth, Vomiting;
- General disorders and administration site conditions: Fatigue, Fever, Injection site inflammation, Oedema;
- Immune system disorders: Angioedema, Hypersensitivity (severe reactions characterized by dyspnea, hypotension, bradycardia, asthenia, and vomiting);
- Musculoskeletal and connective tissue disorders: Transient arthritis;
- Nervous system disorders: Dizziness, Seizures (shortly after administration), Syncope;
- Vascular disorders: Flushing, Hypotension;
- Skin and subcutaneous disorders: Rash, Pruritus, Urticaria.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The use of proton pump inhibitors has been shown to be associated with gastric wall uptake. Gastric wall proximity to the inferior myocardial wall may lead to either false-negative or false-positive findings resulting in an inaccurate diagnosis. Therefore, interruption of proton pump inhibitor therapy for at least 3 days prior to the use of this product in cardiac imaging procedures is recommended.

9.3 Drug-Behavioural Interactions

No data available.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

The use of proton pump inhibitors has been shown to be associated with gastric wall uptake. Gastric wall proximity to the inferior myocardial wall may lead to either false-negative or false-positive findings resulting in, an inaccurate diagnosis. Therefore, interruption of proton pump inhibitor therapy for at least 3 days prior to the use of this product in cardiac imaging procedures is recommended.

Table 9: Established or Potential Drug-Drug Interactions.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Proton Pump Inhibitor therapy drugs	CT	Gastric Wall uptake	Gastric wall proximity to the inferior myocardial wall may lead to either false-negative or false-positive findings, resulting in an inaccurate diagnosis.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions affecting laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Technetium Tc 99m Sestamibi is a cationic Tc 99m complex which has been found to accumulate in viable myocardial tissue in proportion to regional blood flow, in a manner analogous to that of Thallous Chloride Tl-201.

Animal cross-over experiments using Tl 201 and Tc 99m Sestamibi have confirmed that the myocardial distribution of Tc 99m Sestamibi correlates well with regional myocardial perfusion. Scintigraphic images obtained in animals and humans after the intravenous administration of the drug have been comparable to those obtained with Thallous Chloride Tl 201 in normal and infarcted myocardial tissue.

10.2 Pharmacodynamics

No data available.

10.3 Pharmacokinetics

Absorption: No data available.

Distribution: Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast-clearing component clears with a $t_{1/2}$ of 4.3 minutes at rest, and clears with a $t_{1/2}$ of 1.6 minutes under exercise conditions. At five minutes post injection about 8% of the injected dose remains in circulation. There is less than 1% protein binding of Technetium Tc 99m Sestamibi in plasma. The myocardial biological half-life is approximately seven hours after a rest or exercise injection. The biological half-life for the liver is approximately 35 minutes after a rest or exercise injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake. There is no evidence for change in myocardial distribution (redistribution), therefore imaging at delayed times is possible.

Myocardial uptake which is coronary flow dependent is 1.5% of the injected dose during exercise and 1.2% of the injected dose at rest. Animal studies have shown that uptake is not blocked when the sodium pump mechanism is inhibited.

Metabolism: The agent is excreted without any evidence of metabolism.

Elimination: The major metabolic pathway for clearance of Tc 99 Sestamibi is the hepatobiliary system. Activity from the gallbladder appears in the intestines within one hour of injection. Twenty-seven percent (27%) of the injected dose is excreted in the urine, and approximately 33% of the injected dose is cleared through the feces in 48 hours.

Special Populations and Conditions: Special populations and conditions have not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Kit for the Preparation of Technetium Tc 99m Sestamibi Injection should be stored at 15°C to 25°C before and after reconstitution. Protect from light prior to reconstitution. Expiration of the unreconstituted kit is 24 months. Expiration after reconstitution is 6 hours. DO NOT use the kit beyond the expiration date stamped on the box.

Remaining product and components should be disposed of in a safe manner, in compliance with applicable regulations. Refer to Section 12 SPECIAL HANDLING INSTRUCTIONS.

12 SPECIAL HANDLING INSTRUCTIONS

As with any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

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.

Aseptic techniques and effective shielding should be employed in withdrawing doses for administration to patients. Waterproof gloves should be worn during the administration procedure.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Potential radioactive components or remaining product should be, whenever possible, safely stored for decay until they meet unconditional clearance levels per SOR/2000-207 as prescribed by Canada Nuclear Safety Commission. When unconditional clearance levels cannot be achieved, the radioactive waste should be disposed as approved by Canadian Nuclear Safety Commission and/or other applicable authority.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

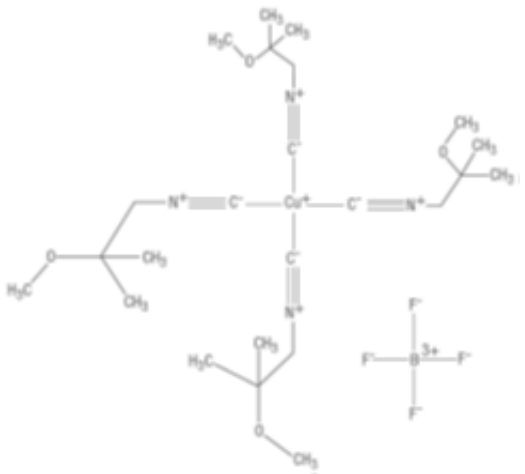
Drug Substance

Proper name: Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Chemical name: Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate.

Molecular formula and molecular mass: $C_{24}H_{44}N_4O_4BF_4Cu$, and molecular mass: 602.98 g/mol.

Structural formula:



Physicochemical properties: Technetium Tc 99m decays by isomeric transition with physical half-life of 6.02 hours.

Product Characteristics:

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. Photons that are useful for detection and imaging studies are listed in **Table 10**.

Table 10: PRINCIPAL RADIATION EMISSION DATA (Kocher, David C., Radioactive Decay Tables, DOE/TIC-11026, 108(1981)).

Radiation	Mean % / Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

No data available.

14.2 Study Results

No data available.

14.3 Comparative Bioavailability Studies

The following study compared the biodistribution of a generic formulation of technetium Tc 99m labelled Sestamibi (MIBI) with the innovator formulation of Technetium Tc 99m labelled Sestamibi, Cardiolite®. In this study, rats (3 males and 3 females) were randomized to 1 of 8 treatment/time point groups. Each rat was injected with approximately 50 µCi of either generic MIBI or Cardiolite. Animals were euthanized at 0.5, 1, 6 or 24 hours after injection of radioactivity. After euthanasia, the following organs or tissues were collected and the amount of radioactivity present measured: liver, lungs, heart, spleen, kidneys, testes/ovaries, skeletal muscle, bone, urinary bladder, urine, stomach wall, small intestine, large intestine, cecum, feces, blood and site of injection. Data from this study demonstrate that the biodistribution of generic MIBI and Cardiolite are equivalent.

Dosing: Each animal was dosed at a volume of 0.2 mL which contained 66.7 µg, and 50 µCi/rat.

Methodology: A single intravenous bolus injection of either the generic formulation of MIBI or the innovator formulation of Cardiolite was administered via the lateral tail vein injection to six Sprague-Dawley rats. After injection, rats were placed in metabolism cages until the time of sacrifice. Animals were sacrificed at 30 minutes and 1, 6, and 24 hours after injection via cervical dislocation. Urine was collected from each rat at sacrifice. The organs, tissue/fluid specimens or excreta from multiple sites were collected and assayed for radioactivity.

Biodistribution comparison: The biodistribution (percent injected dose per gram) data for both products are comparable in all organs at both time points tested as shown in following **Tables 11** and **12**. At one hour post-administration (**Table 11**), compared to Cardiolite, there were statistically significant differences in the biodistribution of generic MIBI. The concentration of generic MIBI was slightly higher in lung, bone, and urine ($P < 0.05$). At six hours post administration, there were no statistically significant differences in the biodistribution of Cardiolite and Curium Sestamibi (**Table 12**).

Table 11: One Hour Biodistribution Data.

Cardiolite vs. Generic MIBI								
1 Hour Data, %ID/g								
	Both Sexes							
	Generic MIBI		Cardiolite		Males – Generic MIBI	Males-Cardiolite	Females-Generic MIBI	Females-Cardiolite®
	Mean	SD	Mean	SD	Mean/SD	Mean/SD	Mean/SD	Mean/SD
Organ/Tissue								
Blood	0.0141	0.0021	0.0136	0.0037	0.0133/0.0003	0.0145/0.0055	0.0149/0.0030	0.0128/0.0012
Liver	0.4687	0.2036	0.3564	0.0396	0.4217/0.098	0.3642/0.0472	0.5157/0.2956	0.3487/0.0387
Kidney	1.7225	0.5356	1.2621	0.5410	1.3569/0.3284	0.907/0.2369	2.088/0.4564	1.6171/0.5454
Heart	3.1785	0.3801	3.0508	0.5683	2.9854/0.2325	2.6892/0.524	3.3716/0.4418	3.423/0.3753
Lung*	0.4827	0.0614	0.3517	0.0381	0.5014/0.0733	0.3524/0.0527	0.4641/0.0550	0.3510/0.0291
Spleen	0.4895	0.0836	0.3995	0.0755	0.4806/0.0460	0.3436/0.0275	0.4985/0.1229	0.4553/0.0642
Muscle	0.5565	0.1001	0.5562	0.1068	0.5037/0.1093	0.5401/0.0371	0.6093/0.0689	0.5722/0.1624
Bone*	0.2258	0.0306	0.1823	0.0331	0.2431/0.0322	0.1705/0.0356	0.2084/0.0201	0.1941/0.0325
Stomach	0.6436	0.0743	0.5734	0.1105	0.6489/0.1001	0.5187/0.0925	0.6384/0.0607	0.6281/0.1140
Sm. Int.	1.8429	0.1918	1.8442	0.7066	1.7475/0.1855	1.2200/0.1030	1.9384/0.1737	2.4685/0.2619
Lg. Int.	0.4657	0.0819	0.3763	0.1368	0.3992/0.0468	0.2812/0.1176	0.5322/0.0361	0.4715/0.0764
Cecum	0.5154	0.1265	0.4160	0.1882	0.5773/0.0635	0.2559/0.0786	0.4536/0.1564	0.5762/0.0739
Gonads	0.3914	0.4318	0.2982	0.3122	0.0273/0.0091	0.0275/0.0020	0.7555/0.2615	0.5690/0.1542
Bladder	0.6957	0.5907	0.8487	0.8309	1.0156/0.7379	1.3114/1.0303	0.3758/0.1441	0.3860/0.1489
Inj. Site	0.4672	0.4286	0.1911	0.0554	0.5875/0.6331	0.2038/0.0689	0.3469/0.1229	0.1783/0.0493
Urine*	0.2383	0.0344	0.1245	0.0544	0.2659/0.0247	0.1085/0.0335	0.2107/0.0079	0.1404/0.0742

***denotes significant differences (P<0.05) between the generic MIBI group and the Cardiolite group by student's t-test.**

Table 12: Six Hour Biodistribution Data.

Cardiolite vs. Generic MIBI								
6 Hour Data, % ID/g								
	Both Sexes							
	Generic MIBI		Cardiolite		Males – Generic MIBI	Males - Cardiolite	Females - Generic MIBI	Females - Cardiolite
	Mean	SD	Mean	SD	Mean/SD	Mean/SD	Mean/SD	Mean/SD
Organ/Tissue								
Blood	0.0056	0.0030	0.0056	0.0033	0.0062/0.0013	0.0074/0.0023	0.0051/0.0044	0.0038/0.0033
Liver	0.1002	0.0387	0.0748	0.0141	0.0807/0.0198	0.0645/0.0051	0.1198/0.0471	0.0850/0.0125
Kidney	0.5994	0.1407	0.5350	0.0757	0.5351/0.0645	0.4744/0.0459	0.6637/0.1814	0.5957/0.0345
Heart	2.8825	0.4371	2.4945	0.2951	2.6170/0.4619	2.2286/0.0443	3.1481/0.2298	2.7604/0.0599
Lung	0.1153	0.0230	0.1115	0.0143	0.1092/0.0101	0.1120/0.0138	0.1215/0.0334	0.1109/0.0180
Spleen	0.0971	0.0146	0.0976	0.0113	0.0973/0.0085	0.1018/0.0159	0.0968/0.0215	0.0934/0.0038
Muscle	0.6905	0.1030	0.6071	0.1801	0.6994/0.0744	0.4955/0.1582	0.6815/0.1441	0.7207/0.1344
Bone	0.0830	0.0172	0.0808	0.0150	0.0848/0.0217	0.0840/0.0123	0.0812/0.01601	0.0776/0.0195
Stomach	0.4245	0.0792	0.4032	0.0588	0.4113/0.0724	0.4109/0.0677	0.4376/0.0996	0.3955/0.0623
Sm. Int.	0.4280	0.1073	0.3446	0.1103	0.3820/0.0782	0.2703/0.0521	0.4739/0.1279	0.4190/0.1054
Lg. Int.	3.3495	1.0090	3.0252	1.0066	2.8055/0.5190	2.5158/0.8001	3.8935/1.1781	3.5345/1.0556
Cecum	5.7852	1.9189	4.8287	1.8961	4.1980/0.9791	3.1459/0.4327	7.3723/0.8304	6.5106/0.5614
Gonads	0.1580	0.1336	0.1940	0.1769	0.0372/0.0121	0.0336/0.0064	0.2788/0.0269	0.3544/0.0310
Bladder	0.2785	0.1586	0.3012	0.3379	0.3931/0.1478	0.3929/0.5035	0.1638/0.0400	0.2094/0.0822
Inj. Site	0.2172	0.0631	0.1526	0.0875	0.2124/0.0963	0.1313/0.0328	0.2219/0.0247	0.1739/0.1293
Urine	0.3907	0.1706	0.2965	0.1047	0.5221/0.0921	0.3363/0.1434	0.2594/0.1120	0.2568/0.0461

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Acute intravenous toxicity studies with male and female mice, rats and dogs and 28 day repeat dose intravenous toxicity studies with male and female rats and dogs were performed. These studies demonstrate that it is safe to administer Technetium Tc 99m Sestamibi to humans under the intended conditions of clinical use. Acute toxicity of the kit was observed only at dose equivalents

of approximately 500 times the maximum human dose. During repeat dose studies, only minimal systemic toxicity and local irritation effects were observed with 28 consecutive daily doses of 150 times the maximum human single dose. At termination, thorough pathological examinations revealed no organ specific abnormalities.

Carcinogenicity: No long-term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc 99m Sestamibi affects fertility in males or females.

Genotoxicity: The active intermediate, $Cu(MIBI)_4BF_4$, was evaluated for genotoxic potential. No genotoxic activity was observed in the Ames, CHO/HPRT and sister chromatid exchange tests (all *in vitro*). At cytotoxic concentrations (≥ 20 µg/mL), an increase in cells with chromosome aberrations was observed in the *in vitro* human lymphocyte assay. $Cu(MIBI)_4BF_4$ did not show genotoxic effects in the *in vivo* mouse micronucleus test at a dose which caused systemic and bone marrow toxicity (9 mg/kg, > 600 X maximal human dose).

Reproductive and Developmental Toxicology: As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

Special Toxicology: No data available.

Juvenile Toxicity: No data available.

16.1 Comparative Non-Clinical Pharmacology and Toxicology

Technetium Tc 99m Sestamibi is a cationic Tc 99m complex which has been found to accumulate in viable myocardial tissue in proportion to regional blood flow, in a manner analogous to that of Thallous Chloride Tl-201.

Animal cross-over experiments using Tl-201 and Tc 99m Sestamibi have confirmed that the myocardial distribution of Tc 99m Sestamibi correlates well with regional myocardial perfusion.

Scintigraphic images obtained in animals and humans after the intravenous administration of the drug have been comparable to those obtained with Thallous Chloride Tl-201 in normal and infarcted myocardial tissue.

The major metabolic pathway for clearance of Tc 99m Sestamibi is the hepatobiliary system; activity from the gallbladder appears in the intestines within one hour of injection. Twenty-seven percent (27%) of the injected dose is excreted in the urine, and approximately 33% of the injected dose is cleared through the feces in 48 hours. The agent is excreted without any evidence of metabolism.

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast-clearing component clears with a $t_{1/2}$ of 4.3 minutes at rest, and clears with a $t_{1/2}$ of 1.6 minutes under exercise conditions. At five minutes post injection about 8% of the injected dose remains in circulation. There is less than 1% protein binding of Technetium Tc 99m Sestamibi in plasma. The myocardial biological half-life is approximately seven hours after a rest or exercise injection. The biological half-life for the liver is approximately 35 minutes after a rest or exercise injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake. There is no evidence for change in myocardial distribution (redistribution), therefore imaging at delayed times is possible.

Myocardial uptake which is coronary flow dependent is 1.5% of the injected dose at exercise and 1.2% of the injected dose at rest. Animal studies have shown that uptake is not blocked when the sodium pump mechanism is inhibited.

16.1.1 Comparative Non-Clinical Pharmacodynamics

No data available.

16.1.2 Comparative Toxicology

No data available.

17 SUPPORTING PRODUCT MONOGRAPHS

Cardiolite ®, Powder for Solution, 1.0 mg/vial, submission control 124915, Product Monograph, Lantheus MI Canada. DEC 11,2008.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

KIT FOR THE PREPARATION OF TECHNETIUM Tc 99m SESTAMIBI INJECTION

Read this carefully before you receive an injection of **Technetium Tc 99m Sestamibi**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about the **Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.**

Serious Warnings and Precautions
Only health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans should use radiopharmaceuticals.

What is the Kit for the Preparation of Technetium Tc 99m Sestamibi Injection used for?

- To study blood circulation in the heart;
- To determine if any areas of the heart muscle have been damaged due to an insufficient blood supply to the heart;
- For diagnostic use only.

How does Technetium Tc 99m Sestamibi Injection work?

Technetium Tc 99m Sestamibi Injection is a medicinal product which contains a radioactive medicine. Once the medicine is injected, your doctor will take a picture (scan) of your heart. The area where the radioactive compound accumulated will show up in the image and help your doctor decide if there is a problem with your heart.

What are the ingredients in the Kit for the Preparation of Technetium Tc 99m Sestamibi Injection?

Medicinal ingredients: Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) Tetrafluoroborate.

Non-medicinal ingredients: L-Cysteine Hydrochloride Monohydrate; Mannitol; Sodium Citrate Dihydrate; Stannous Chloride Dihydrate and Tin Chloride Dihydrate.

The Kit for the Preparation of Technetium Tc 99m Sestamibi Injection comes in the following dosage forms:

Powder for solution.

Do not use the Kit for the Preparation of Technetium Tc 99m Sestamibi Injection if:

There are no known contraindications however your exam may include a part where you will be asked to exercise or take medication to increase your heart rate; tell your healthcare professional should you have difficulties with physical activities or are allergic to any medication.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive the Technetium Tc 99m Sestamibi Injection. Talk about any health conditions or problems you may have, including if:

- There is a possibility that you may be pregnant;
- You are breastfeeding;
- You are taking any other heart medications;
- You had an allergic reaction to this drug or you had an imaging study with this drug before.

Contamination

The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product:

- Toilet should be used instead of urinal;
- Toilet should be flushed several times after use;
- If blood or urine gets onto clothing, such clothing should be washed separately or stored for 1 to 2 weeks to allow for decay and then wash.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

Other warnings you should know about:

Technetium Tc 99m Sestamibi has been rarely associated with acute severe allergic and anaphylactic events (a rare allergic response) of angioedema (swelling of the face and lips) and generalized urticaria (hives). See "What are the possible side effects from receiving Technetium Tc 99m Sestamibi Injection?".

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with the Kit for the Preparation of Technetium Tc 99m Sestamibi Injection:

Medicines classified as proton pump inhibitors are used to reduce stomach acid and may possibly interfere with the use of this product when obtaining a picture of the heart. Discuss with your doctor or pharmacist whether you should stop taking a proton pump inhibitor 3 days before the day of the scan and before receiving Technetium Tc 99m Sestamibi Injection.

How to receive Technetium Tc 99m Sestamibi:

Technetium Tc 99m Sestamibi Injection will be administered to you by a healthcare professional who is experienced in the use of radiopharmaceuticals.

Usual dose:

Depending on your exam, you will receive a dose calculated for you. The suggested dose range for intravenous administration in the average patient (70 kg) is: 370-1110 MBq (10 – 30 mCi).

Overdose:

If you think you, or a person you are caring for, have received too much Technetium Tc 99m Sestamibi, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms. Drink liquids to increase your amount of urination to help remove the drug from your body.

Missed Dose:

Since you will receive Technetium Tc 99m Sestamibi Injection specially calculated for you by a health care professional there is no missed dosing.

What are possible side effects from receiving Technetium Tc 99m Sestamibi Injection?

These are not all the possible side effects you could have when receiving Technetium Tc 99m Sestamibi Injection. If you experience any side effects, tell your healthcare professional.

Most common side effects include taste and smell perversion and dry mouth. Headaches may occur but are uncommon.

Serious side effects are rare but include chest pain, heartbeat changes which may occur during procedures being conducted, sore joints, seizure; and hypersensitivity, a rare allergic response characterized by being short of breath, low blood pressure, slower heartbeat, weakness and vomiting which occur after two hours of a second injection of Tc 99m Sestamibi. In those cases, your doctor should be alerted and will help manage the situation.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Call your doctor or pharmacist immediately
	Only if severe	In all cases	
COMMON			
Chest pain / angina			X
ST segment changes (heartbeat changes)			X
Taste perversion	X		
RARE			
Headache	X		
Nausea	X		
Parosmia (change in sense of smell)	X		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Call your doctor or pharmacist immediately
	Only if severe	In all cases	
Signs and symptoms consistent with seizure			X
Transient arthritis (sore joints)		X	
Angio-Edema (swelling of the face and lips			X
Arrhythmia (change in the heartbeat)			X
Dizziness	X		
Syncope (low blood pressure)			X
Vomiting	X		
Abdominal pain	X		
Pruritis (itching)		X	
Rash			X
Urticaria (hives)			X
Hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthenia and vomiting within two hours after a second injection of Technetium Tc 99m Sestamibi (An allergic response involving shortness of breath, slowing of the heartbeat, weakness, and vomiting)			X
Flushing	X		
Edema (swelling, as water retention)	X		
Inflammation of the injection site	X		
Dry mouth	X		
Fever	X		
Fatigue	X		
Any other symptoms		X	X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

The Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is stored at 15°C to 25°C before and after reconstitution.

If you want more information about the Kit for the Preparation of Technetium Tc 99m Sestamibi Injection:

- Talk to your healthcare professional; and/or
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.curiumpharma.com, or by calling 1-800-885-5988.

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