PRODUCT MONOGRAPH

CARDIOLITE®

(Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

Radiodiagnostic Agent

(Myocardial Imaging)

Manufacturer:
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(Kit for the Preparation of Technetium Tc99m Sestamibi for Injection)

THERAPEUTIC CLASSIFICATION

Radiodiagnostic Agent
(Myocardial Imaging)

ACTION AND CLINICAL PHARMACOLOGY

Each 5mL vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Tetrakis (2-methoxy isobutyl isonitrile) Copper (1) tetrafluoroborate	1.0 mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2$.$2H_2O$)	0.025 mg
Sodium Citrate Dihydrate	2.6 mg
Total Tin, maximum ($SnCl_2$. $2H_2O$)	0.086 mg
L-Cysteine Hydrochloride Monohydrate	1.0 mg
Mannitol	20 mg

Prior to lyophilization the pH is 5.3 to 5.9. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection. The pH of the reconstituted product is 5.5 (5.0-6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is Tc99m $[MIBI]^+_6$ where MIBI is 2-methoxy isobutyl isonitrile.

PHYSICAL CHARACTERISTICS

Technetium Tc99m 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 1.

TABLE 1

PRINCIPLE RADIATION EMISSION DATA

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

*Kocher, David C., Radioactive Decay Data Tables, DOE/TIC-11026, 108(1981).

EXTERNAL RADIATION

The specific gamma ray constant for Tc99m 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 2. 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 2

RADIATION ATTENUATION BY LEAD SHIELDING

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

TABLE 3

Physical Decay Chart; Tc99m Half-Life 6.02 Hours

Hours	Fraction Remaining
0*	1.000
1	.891
2	.794
3	.708
4	.631
5	.562
6	.501
7	.447
8	.398
9	.355
10	.316
11	.282
12	.251

* Calibration time

CLINICAL PHARMACOLOGY

Technetium Tc99m Sestamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in proportion to regional blood flow, analogous to Thallous Chloride TI-201.

Animal cross-over experiments using TI -201 and Tc99m Sestamibi have confirmed that the myocardial distribution of Tc99m Sestamibi correlates well with regional myocardial perfusion.

Scintigraphic images obtained in animals and man after the intravenous administration of Tc99m Sestamibi have been comparable to those obtained with TI -201 in normal and infarcted myocardial tissue.

The major metabolic pathway for clearance of Tc99m Sestamibi is the hepatobiliary system. Activity from the gallbladder appears in the intestines within one hour of injection. 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 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 $t_{½}$ of 4.3 minutes at rest and clears with a $t_{½}$ of 1.6 minutes under exercise conditions. At five minutes post injection about 8% of the injected dose remains in circulation. The myocardial $t_{½}$ is approximately seven hours after a rest or exercise injection. The $t_{½}$ 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% at rest. Animal studies have shown that uptake is not blocked when the sodium pump mechanism is inhibited.

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 Tc99m 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 pathologic examinations revealed no organ specific abnormalities.

INDICATIONS AND USAGE

Technetium Tc99m 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 Tc99m Sestamibi is also useful in the assessment of global ventricular function by the first pass technique.

CONTRAINDICATIONS

None known.

WARNINGS

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.

The contents of the kit are not radioactive. However, after the sodium pertechnetate Tc99m Injection is added, adequate shielding of the final preparation must be maintained to minimise radiation exposure to occupational workers and patients.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability, should be performed during the first ten days following the onset of menses.

PRECAUTIONS

General

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

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

The components of the reagent vial are sterile and non-pyrogenic. It is essential that the user follow the directions carefully and adheres to strict aseptic techniques.

The Technetium Tc99m labelling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be employed.

Radiopharmaceuticals should be used only by those medical practitioners who are

appropriately qualified in the use of radioactive prescribed substances in or on humans.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc99m Sestamibi affects fertility in males or females. As with other radiopharmaceuticals which distribute intracellularly, there may be an increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

In comparison with most other diagnostic technetium labelled 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).

The active intermediate, $Cu(MIBI)_4BF_4$, was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and sister chromatid exchange test (all *in vitro*). At cytotoxic concentrations ($\geq$ 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).

Use in Pregnancy

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Sestamibi. It is also not known whether Technetium Tc99m 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 Tc99m Sestamibi should be given to a pregnant woman only if clearly needed. Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability, should be performed during the first ten days following the onset of menses.

Nursing Mothers

Technetium Tc99m is excreted in human milk during lactation. It is not known whether Technetium Tc99m Sestamibi is excreted in human milk. Therefore, formula feedings should be substituted for breast feedings.

Pediatric Use

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

ADVERSE REACTIONS

The active ingredient in CARDIOLITE®, Technetium Tc99m Sestamibi, is also marketed under the name MIRALUMA® which is used for breast imaging.

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 reported after receiving Technetium Tc99m Sestamibi administration are shown in the following table:

TABLE 4

Selected Adverse Events Reported in 0.5% of Patients Who Received Technetium Tc99m Sestamibi in Either Breast Or Cardiac Clinical Studies*

Adverse Events	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 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 $\leq$ 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 hypertensivity characterized by dyspnea, hypotension, bradycardia, asthenia and vomiting within two hours after a second injection of Technetium Tc99m-Sestamibi. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, and fatigue have also been attributed to administration of the agent.

DOSAGE AND ADMINISTRATION

The suggested dose range for I.V. administration to be employed in the average patient (70 kg) is: 370-1110 MBq (10-30 mCi).

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%.

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

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

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m SESTAMIBI

Preparation of Technetium Tc99m Sestamibi from the Kit for the preparation of Technetium Tc99m Sestamibi for Injection is done by the following aseptic procedure:

a) Prior to adding the Sodium Pertechnetate Tc99m 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 Tc99m Injection [max. 5.6 GBq (150 mCi)] in approximately 1 to 3 mL.

e) Aseptically add the Sodium Pertechnetate Tc99m 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 a boiling water bath for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again. Do not allow the boiling water bath 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 fifteen minutes.

i) Using proper shielding, the vial containing the reconstituted solution should be

visually inspected for particulates and/or discoloration prior to injection.

j) Complete and affix the "radioactive contents" label to the vial shield.

k) Aseptically withdraw material for use within six (6) hours. Store the reconstituted vial at 15-25°C. The vial contains no preservative.

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

DETERMINATION OF RADIOCHEMICAL PURITY IN TECHNETIUM Tc99m 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 Tc99m Sestamibi solution, side by side on top of the ethanol* spot. Return the plate to the 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 Tc99m activity in each piece by appropriate radiation detector.

8. Calculate the % Tc99m Sestamibi as:

$$\% \text{ Tc99m Sestamibi} = \frac{\mu\text{Ci Top Piece}}{\mu\text{Ci Both Pieces}} \times 100$$

9. The dose should contain Tc99m Sestamibi ≥ 90%. Do not use if radiochemical purity is less than 90%.

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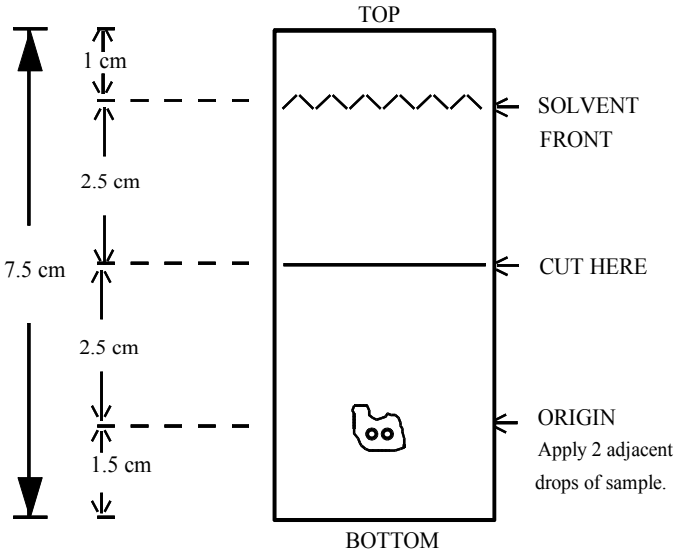
*The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99%) should remain at ≥ 95% ethanol content for one week after opening if stored tightly capped, in a cool dry place.

TLC PLATE DIAGRAM



RADIATION DOSIMETRY

The radiation doses to organs and tissues of an average patient (70 kg) per 1110 MBq (30 mCi) of Technetium Tc99m Sestamibi injected intravenously are shown in Table 5.

TABLE 5

RADIATION DOSE ESTIMATES FOR Tc99m SESTAMIBI
Estimated Radiation Absorbed Dose

REST				
	2.0 hours void		4.8 hour void	
Organ	**rads/30mCi**	**mGy/1110MBq**	**rads/30mCi**	**mGy/1110MBq**
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Small Intestine	3.0	30.0	3.0	30.0
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Lower Large Intestine Wall	3.9	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.6	5.8
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
Bone Surfaces	0.7	6.8	0.7	6.4
Thyroid	0.7	7.0	0.7	6.8
Ovaries	1.5	15.5	1.6	15.5
Testes	0.3	3.4	0.4	3.9
Red Marrow	0.5	5.1	0.5	5.0
Urinary Bladder Wall	2.0	20.0	4.2	41.1
Total Body	0.5	4.8	0.5	4.8
	Rem/30mCi	mSv/1110MBq	rem/30mCi	mSv/1110MBq
Effective Dose Equivalent	1.5	15.5	1.7	16.7
STRESS				
	2.0 hours void		**4.8 hour void**	
Organ	**rads/30mCi**	**mGy/1110MBq**	**rads/30mCi**	**mGy/1110MBq**
Breasts	0.2	2.0	0.2	1.8
Gallbladder Wall	2.8	28.9	2.8	27.8
Small Intestine	2.4	24.4	2.4	24.4

STRESS				
	2.0 hours void		4.8 hour void	
Organ	**rads/30mCi**	**mGy/1110MBq**	**rads/30mCi**	**mGy/1110MBq**
Upper Large Intestine Wall	4.5	44.4	4.5	44.4
Lower Large Intestine Wall	3.3	32.3	3.3	32.2
Stomach Wall	0.5	5.3	0.5	5.2
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
Bone Surfaces	0.6	6.2	0.6	6.0
Thyroid	0.3	2.7	0.2	2.4
Ovaries	1.2	12.2	1.3	13.3
Testes	0.3	3.1	0.3	3.4
Red Marrow	0.5	4.6	0.5	4.4
Urinary Bladder Wall	1.5	15.5	3.0	30.0
Total Body	0.4	4.2	0.4	4.2
	Rem/30mCi	mSv/1110MBq	rem/30mCi	mSv/1110MBq
Effective Dose Equivalent	1.3	13.3	1.4	14.4

Stabin, M., July, 1990, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831, (423) 576-3449.

HOW SUPPLIED

CARDIOLITE® Kit for the preparation of Technetium Tc99m Sestamibi for Injection is supplied as a 5mL vial in kits of two (2), five (5), twenty (20) and thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is between 5.3-5.9. The contents of the vial are lyophilized and stored under nitrogen. Store at 15-25°C before and after reconstitution. Technetium Tc99m Sestamibi contains no preservatives. Included in each two (2) vial kit is one (1) package insert and six (6) radiation labels. Included in each five (5) vial kit is one (1) package insert and twelve (12) radiation labels. Included in each twenty (20) vial kit is one (1) package insert and forty-eight (48) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and seventy-two (72) radiation labels.