



ENGLISH

DRAXIMAGE® Sestamibi

Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

Radiodiagnostic Agent
(Myocardial Imaging)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Injection	1.0 mg/vial	None. For a complete listing see Dosage Forms, Composition and Packaging section.

DESCRIPTION

Physical Characteristics
Technetium Tc 99m decays by isomeric transition with physical half-life of 6.02 hours¹. 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

External Radiation

The specific gamma ray constant for Tc 99m is 5.4 microcurie/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 the 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; Tc 99m 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

INDICATIONS AND CLINICAL USE

- DRAXIMAGE® Sestamibi is indicated for:
 - myocardial perfusion imaging for the diagnosis and localization of myocardial infarction
 - diagnosis and localization of ischemic heart disease and coronary artery disease
 - assessment of global ventricular function by the first pass technique

CONTRAINDICATIONS

None known.

WARNINGS AND PRECAUTIONS

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.

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 Tc 99m Injection is added, adequate shielding of the final preparation must be maintained to minimize radiation exposure to occupational workers and patients.

Ideally, examination 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.

General

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.

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 minimize 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 Tc 99m labelling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Hence, Sodium Pertechnetate Tc 99m 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 Tc 99m 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 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).

The active intermediate, Cu(MIBI)₂BF₄, 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 concentration (≥ 20 µg/mL), an increase in cells with chromosome aberrations was observed in the *in vitro* human lymphocyte assay. Cu(MIBI)₂BF₄ 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).

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.

Special Populations

Pregnant Women

Animal reproduction and teratogenicity 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. There have been no studies in pregnant women. Technetium Tc 99m Sestamibi should be given to a pregnant woman only if clearly needed. Ideally, examination 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 Women

Technetium Tc 99m 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 breast feedings.

Pediatric

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

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

TABLE 4
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		Total n=3046
	Women n=673	Women n=695	Men n=2361	Men n=2361	
Headache	11 (1.6%)	2 (0.3%)	4 (0.2%)	6 (0.2%)	6 (0.2%)
Chest Pain / Angina	0 (0%)	18 (2.6%)	46 (1.9%)	64 (2.1%)	64 (2.1%)
ST segment changes	0 (0%)	11 (1.6%)	29 (1.2%)	40 (1.3%)	40 (1.3%)
Nausea	4 (0.6%)	1 (0.1%)	2 (0.1%)	3 (0.1%)	3 (0.1%)
Taste Perversion	129 (19.2%)	60 (8.6%)	157 (6.6%)	217 (7.1%)	217 (7.1%)
Parosmia	8 (1.2%)	6 (0.9%)	10 (0.4%)	16 (0.5%)	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 dyspnea, hypotension, bradycardia, asthenia and vomiting within two hours after a second injection of Technetium Tc 99m Sestamibi. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, and fatigue have also been attributed to administration of the agent.

It should be noted that the above data on Adverse Events Reported in Breast Studies is provided for safety information purposes; the DRAXIMAGE® Sestamibi product is not indicated for breast imaging.

DOSAGE AND ADMINISTRATION

Dosage

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

Administration

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 2 – 25°C before reconstitution and 15 – 25°C after reconstitution.

Instructions for Preparation and Use

Preparation of 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.

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 [max. 5.6 GBq (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 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 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 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 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.

¹Kocher, David C., Radioactive Decay Data Tables, DOE/TIC-11026, 108(1981).

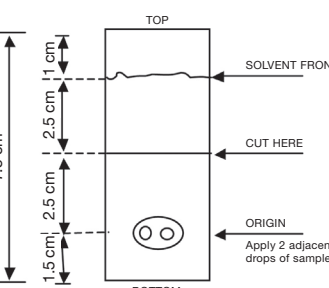
*The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99%) should remain at ≥ 95% ethanol content for one week after opening if stored tightly capped, in a cool dry place.

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:

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

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



ACTION AND CLINICAL PHARMACOLOGY

Technetium Tc 99m Sestamibi is cationic Tc 99m complex which has been found to accumulate in viable myocardial tissue in proportion to regional blood flow, analogous to 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 man after the intravenous administration of Tc 99m Sestamibi have been comparable to those obtained with 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 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_{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. The myocardial t_{1/2} is approximately seven hours after a rest or exercise injection. The t_{1/2} 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.

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 in Table 5.

TABLE 5
Radiation Dose Estimates for Tc 99m Sestamibi
Estimated Radiation Absorbed Dose

Organ	REST			
	2.0 hours void		4.8 hour void	
	rads/30 mCi	mGy/1110 MBq	rads/30 mCi	mGy/1110 MBq
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/30 mCi	mSv/1110 MBq	rem/30 mCi	mSv/1110 MBq
Effective Dose Equivalent	1.5	15.5	1.7	16.7

Organ	STRESS			
	2.0 hours void		4.8 hours void	
	rads/30 mCi	mGy/1110 MBq	rads/30 mCi	mGy/1110 MBq
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
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/30 mCi	mSv/1110 MBq	rem/30 mCi	mSv/1110 MBq
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.

COMPARATIVE ANIMAL BIODISTRIBUTION

The purpose of this study is to compare the biodistribution in rats of DRAXIMAGE® Sestamibi with that of Cardiolite® since DRAXIMAGE® Sestamibi is a generic version of Cardiolite® (Lantheus Medical Imaging).

Dosing

A dose of 50 µCi was used for each rat.

Reconstitution of vials

One vial of each product was reconstituted with 25 mCi Tc-99m in 3 mL of saline. Approximately 1.0 mCi of the reconstituted products was diluted in 9.9 mL of saline.

Methodology

The diluted reconstituted radiopharmaceuticals were administered by tail vein injection (0.5 mL per rat) to Sprague-Dawley male rats (28 rats per formulation for 1 hour timepoint and 14 rats per formulation for 6 hours timepoint). Animals were sacrificed 1 and 6 hr after radiopharmaceutical administration by CO₂ asphyxiation. Blood was taken immediately after sacrifice by cardiac puncture and dissection to remove the indicated tissues was performed. Dissected tissues were rinsed under running water, blotted, weighed and then placed in counting tubes for Tc-99m counting in a gamma counter.

Biodistribution comparison

The biodistribution (percent injected dose per gram) data for both products are comparable in all organs and at both time points tested as shown in following Tables 6 and 7. At one hour post-administration, there were no significant differences in the biodistribution of Cardiolite® and DRAXIMAGE® Sestamibi. At 6 hours (Table 7), compared to Cardiolite®, the concentration of DRAXIMAGE® Sestamibi was 0.01% slightly higher in the liver (p=0.018), and 0.09% higher in the kidney (p=0.004). There were no other statistically significant differences.

TABLE 6
Comparison of Biodistribution in rats of Cardiolite®
and DRAXIMAGE® Sestamibi at 1 hour

	Mean Cardiolite® %ID/g	Mean DRAXIMAGE® Sestamibi %ID/g	Difference in means	LL CI95%	UL CI95%	p
Blood	0.018	0.015	0.002	-0.000	0.005	0.054
Liver	0.281	0.291	-0.010	-0.033	0.052	0.657
Kidney	1.732	1.817	-0.085	-0.124	0.295	0.417
Stomach	0.334	0.315	0.018	-0.051	0.087	0.598
Intestine	1.256	1.235	0.021	-0.160	0.201	0.821
Muscle	0.437	0.480	-0.043	-0.017	0.103	0.154
Thyroid	0.439	0.491	-0.052	-0.017	0.122	0.139
Spleen	0.463	0.491	-0.028	-0.051	0.107	0.481
Lung	0.229	0.242	-0.013	-0.015	0.042	0.346
Heart	2.010	2.134	-0.124	-0.083	0.331	0.236