PRODUCT MONOGRAPH

DRAXIMAGE® Sestamibi
Kit for the Preparation of Technetium Tc 99m Sestamibi Injection

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

1.0 mg per vial, Freeze-dried powder

Professed standard

Radiodiagnostic Agent (Myocardial Imaging)

ATC Code: V09GA01

Jubilant DraxImage Inc.
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PRODUCT MONOGRAPH

DRAXIMAGE® Sestamibi
(Kit for the Preparation of Technetium Tc 99m Sestamibi Injection)

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 hours[1]. Photons that are useful for detection and imaging studies are listed in Table 1.

TABLE 1

Principle Radiation Emission Data

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

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

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 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	0.891
2	0.794
3	0.708
4	0.631
5	0.562
6	0.501
7	0.447
8	0.398
9	0.355
10	0.316
11	0.282
12	0.251

* 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 ischaemic 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, $Cu(MIBI)_4BF_4$, 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 concentration ($\geq$ 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).

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

Cases of parathyroid uptake of 99mTc-sestamibi have been reported in the literature.

Clinical Trial Adverse Drug Reactions

Adverse events were evaluated in 3 741 adults who were evaluated in clinical studies. Of these patients, 3 068 (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*

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 ≤ 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 – 1 110 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 to 25 °C before reconstitution and 15 to 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 to 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 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 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.

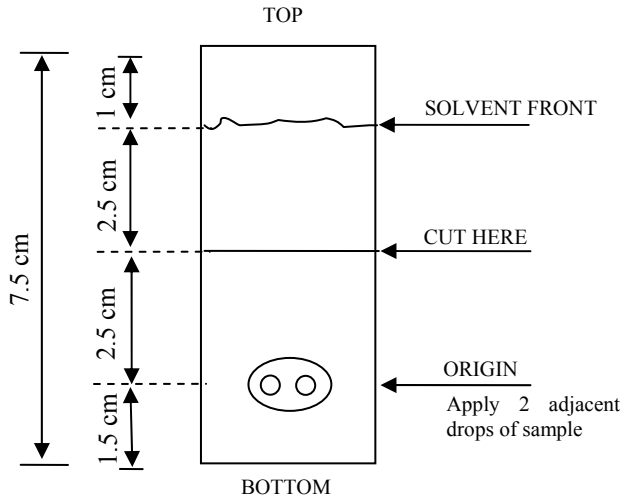
7. Cut the TLC plate 4 cm from the bottom and measure the Tc-99m activity in each piece by appropriate radiation detector.

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 %.

* 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



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 T1-201.

Animal cross-over experiments using T1-201 and ^{99m}Tc-sestamibi have confirmed that the myocardial distribution of ^{99m}Tc-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 T1-201 in normal and infarcted myocardial tissue.

The major metabolic pathway for clearance of ^{99m}Tc-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.

RADIATION DOSIMETRY

Estimates of radiation doses to organs and tissues of an average patient (70 kg) per 1110 MBq (30 mCi) of ^{99m}Tc-sestamibi injected intravenously are shown in Table 5.

TABLE 5

RADIATION DOSE ESTIMATES FOR ^{99m}Tc-SESTAMIBI
Estimated Radiation Absorbed Dose

REST				
	2.0 hours void		4.8 hour void	
Organ	**rads/30 mCi**	**mGy/1 110 MBq**	**rads/30 mCi**	**mGy/1 110 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/1 110 MBq	rem/30 mCi	mSV/1 110 MBq
Effective Dose Equivalent	1.5	15.5	1.7	16.7
STRESS				
	2.0 hours void		4.8 hours void	
Organ	**rads/30 mCi**	**mGy/1 110 MBq**	**rads/30 mCi**	**mGy/1 110 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/1 110 MBq	rem/30 mCi	mSV/1 110 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 CO_2 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

ID: Injected Dose LL: Lower Limit UL: Upper Limit CI: Confidence Interval

TABLE 7

Comparison of Biodistribution in rats of Cardiolite® and DRAXIMAGE Sestamibi at 6 hours

	Mean Cardiolite® % ID/g	*Mean DRAXIMAGE® Sestamibi % ID/g*	*Difference in means*	*LL CI95 %*	*UL CI95 %*	*p*
Blood	0.004	0.005	0.000	-0.001	0.001	0.543
Liver	0.062	0.072	-0.010	0.002	0.018	0.018
Kidney	0.526	0.612	-0.086	0.030	0.142	0.004
Stomach	0.198	0.167	0.031	-0.014	0.076	0.170
Intestine	2.104	2.121	-0.017	-0.192	0.226	0.869
Muscle	0.528	0.509	0.019	-0.043	0.081	0.534
Thyroid	0.459	0.475	-0.016	-0.045	0.077	0.587
Spleen	0.077	0.081	-0.004	-0.001	0.009	0.114
Lung	0.099	0.098	0.001	-0.017	0.019	0.908
Heart	1.710	1.824	-0.114	-0.004	0.232	0.057

ID: Injected Dose LL: Lower Limit UL: Upper Limit CI: Confidence Interval

STORAGE AND STABILITY

Prior to lyophilization the pH is between 5.3 to5.9. The contents of the vial are lyophilized and stored under nitrogen. Store at 2 to 25 °C before reconstitution and 15 to 25 °C after reconstitution. Protect from light. Technetium Tc 99m Sestamibi Injection contains no preservatives.

SPECIAL HANDLING INSTRUCTIONS

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DRAXIMAGE® Sestamibi Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is supplied as a 10 mL vial in kits of two (2), five (5) and ten (10) vials, sterile and non-pyrogenic.

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 ten (10) radiation labels. Included in each ten (10) vial kit is one package insert and twenty (20) radiation labels.

Each 10 mL vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Tetrakis (2-methoxyisobutylisonitrile)copper(I) tetrafluoroborate	1.0 mg
Stannous chloride dihydrate, minimum ($SnCl_2 \cdot 2H_2O$)	0.025 mg
Sodium citrate dihydrate	2.6 mg
Total tin, maximum ($SnCl_2 \cdot 2H_2O$)	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 Tc 99m Injection. The pH of the reconstituted product is 5.5 (5.0 to 6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is $^{99m}Tc\ [MIBI]_6^+$ where MIBI is 2-methoxyisobutylisonitrile.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Tetrakis (2-methoxyisobutylisonitrile)copper(I) tetrafluoroborate

Chemical name: tetrakis (1-isocyano-2-methoxy-2-methylpropyl)copper(I) tetrafluoroborate

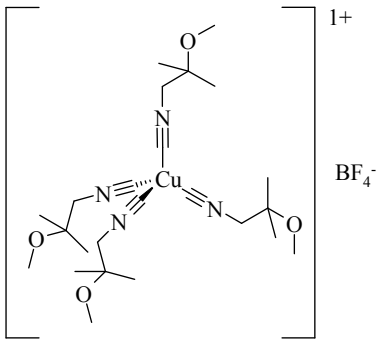
tetrakis (2-methoxyisobutylisonitrile)copper(I) tetrafluoroborate;

tetrakis (1-isocyano-2-methoxy-2-methylpropane)copper(I) tetrafluoroborate;

propane, 1-isocyano-2-methoxy-2-methyl-, copper complex tetrafluoroborate.

Molecular formula and molecular mass: $Cu(C_6H_{11}NO)_4BF_4$ 602.98 g/mol

Structural formula:



Physicochemical properties:

CuMIBI is a white solid powder, slightly soluble in water, soluble in methanol and ethanol, highly soluble in dichloromethane, chloroform and acetone.

Product Characteristics

Physical Characteristics

Technetium Tc 99m decays by isomeric transition with physical half-life of 6.02 hours[2]. Photons that are useful for detection and imaging studies are listed in Table 1.

TABLE 1

Principle Radiation Emission Data

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

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 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}
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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.

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

TABLE 3

Physical Decay Chart; Tc-99m Half-Life 6.02 hours

Hours	Fraction Remaining
0*	1.000
1	0.891
2	0.794
3	0.708
4	0.631
5	0.562
6	0.501
7	0.447
8	0.398
9	0.355
10	0.316
11	0.282
12	0.251

* Calibration time

CLINICAL TRIALS

DETAILED 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 T1-201.

Animal cross-over experiments using T1-201 and ^{99m}Tc-sestamibi have confirmed that the myocardial distribution of ^{99m}Tc-sestamibi correlates well with regional myocardial perfusion.

Scintigraphic images obtained in animals and man after the intravenous administration of ^{99m}Tc-sestamibi have been comparable to those obtained with T1-201 in normal and infracted myocardial tissue.

The major metabolic pathway for clearance of 99mTc-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 $t_{½}$ 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 Tc 99m Sestamibi Injection 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.

REFERENCES

1. Cardiolite® (Kit for the Preparation of Technetium Tc 99m Sestamibi for Injection), Canadian Product Monograph, Date of Authorization: December 11, 2008. (Manufacturer: Lantheus Medical Imaging, N. Billerica, MA, 01862, USA; Distributor: Lantheus MI Canada, Inc, 1111 Frederik-Philips Boulevard, montreal, QC, Canada).

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

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

PART III: CONSUMER INFORMATION

DRAXIMAGE® Sestamibi
(Kit for the Preparation of Technetium Tc 99m Sestamibi Injection)

This leaflet is part III of a three-part "Product Monograph" published when DRAXIMAGE® Sestamibi was authorized for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DRAXIMAGE® Sestamibi. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DRAXIMAGE® Sestamibi is used:

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

What is does:
DRAXIMAGE® Sestamibi is a medicinal product which contains a radioactive medicine. After injecting DRAXIMAGE® Sestamibi your doctor will take an image (scan) of the concerned organ (heart). The area where the radioactive compound accumulated will show up in the scan and help the doctor make the diagnosis.

When it should not be used:
No contraindications are known.

What the medicinal ingredient is:
Tetrakis (2-methoxyisobutylisonitrile)copper(I) tetrafluoroborate

What the important nonmedicinal ingredients are:
DRAXIMAGE® Sestamibi contains no nonmedicinal ingredients.

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.

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.

INTERACTIONS WITH THIS MEDICATION

None.

PROPER USE OF THIS MEDICATION

This product DRAXIMAGE® Sestamibi will be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most common side effects include taste and smell perversion and dry mouth. They are typically self-limiting. Headaches may occur but are uncommon.

Serious side effects are rare but include chest pain, heart beat changes, sore joints, seizure and hypersensitivity, a rare allergic response characterized by shortness of breath, hypotension, slower heart beat, weakness and vomiting which occur within two hours after a second injection of Technetium Tc 99m Sestamibi. In those cases, your doctor should be alerted and will help manage the situation.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Call your doctor or pharmacist
		Only if severe	In all cases	
Common	Chest pain/angina			√
	ST segment changes (heart beat changes)			√
	Taste perversion	√		
Un-common	Headache	√		
	Nausea	√		
	Parosmia (change in sense of smell)	√		
	Signs and symptoms consistent with seizure			√
	Transient arthritis (sore joints)		√	
	Angioedema (swelling of the face and lips)			√
	Arrhythmia (change in the heart beat)			√
	Dizziness	√		
	Syncope			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Call your doctor or pharmacist
		Only if severe	In all cases	
	(low blood pressure)			
	Vomiting	√		
	Abdominal pain	√		
	Pruritis (itching)		√	
	Rash			√
	Urticaria (hives)			√
	Hypersen-sitivity characteri-zed by dyspnea, hypoten-sion, bradycar-dia, 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 heart beat, weakness, and vomiting)			√
	Flushing	√		
	Edema	√		
	Inflammation of the injection site	√		
	Dry mouth	√		
	Fever	√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Call your doctor or pharmacist
		Only if severe	In all cases	
	Fatigue	√		
	Any other symptoms		√	√

This is not a complete list of side effects. If you have any unexpected effects after receiving DRAXIMAGE® Sestamibi, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.draximage.com or by contacting the sponsor, Jubilant DraxImage Inc, at: 1-888-633-5343

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