**STUDY TITLE:**
IMAGING in HF (The Investigation of Myocardial Gated SPECT Imaging in Heart Failure)

**PUBLICATION TITLE:**
Etiology and Pathophysiology of New-Onset Heart Failure: Evaluation by Myocardial Perfusion Imaging

**JOURNAL:**
Journal of Nuclear Cardiology 2009; 16:1; 82-91

**AUTHORS:**

**CONTEXT:** Data from observational studies suggest that up to 70% of patients with heart failure (HF) have coronary artery disease (CAD) as the underlying etiology. However, these data have generally accrued from clinical trials that enrolled patients with chronic HF, and the prevalence of CAD in patients with new-onset HF is less well studied. Optimal initial evaluation strategy of patients presenting with new-onset HF remains unclear. A prospective assessment of performance characteristics of contemporary radionuclide MPI for the diagnosis of CAD in patients with new-onset HF has not been performed.

**OBJECTIVE:** To explore the role of single-photon emission computed tomographic (SPECT) myocardial perfusion imaging (MPI) as an initial investigative strategy in patients hospitalized with new-onset HF.

**DESIGN, SETTING AND PATIENTS:** The IMAGING in Heart Failure study was a prospective, multi-national trial that recruited 201 patients (age 65.3 ± 14.5 years, 43% women) hospitalized with their first episode of heart failure. Rest/stress gated SPECT Tc-99m sestamibi MPI was performed during or within 2 weeks of the index hospitalization, in addition to standard care.

**MAIN OUTCOME MEASURE:** Extensive coronary artery disease

**CARDIOLITE® UTILIZATION:** Cardiolite® was the myocardial perfusion imaging agent selected for use in the IMAGING HF study. 201 patients underwent rest/stress gated SPECT myocardial perfusion imaging with Cardiolite® to evaluate the extent of coronary artery disease in patients hospitalized with new-onset heart failure.

**RESULTS:** SPECT MPI revealed a broad range of ejection fractions with preserved systolic function in 36% of patients. Forty-one percent of patients had normal perfusion. In the remaining patients, perfusion abnormalities were predominantly due to prior myocardial infarction, with extensive ischemia seen only in 6%. Among patients who underwent coronary angiography, SPECT performance characteristics revealed excellent negative predictive value (96%) for extensive coronary artery disease (CAD). In multivariable analyses, the extent of perfusion abnormality and advancing age predicted the presence of extensive CAD.

**CONCLUSIONS:** These preliminary data derived from a non-randomized observational cohort suggest potential diagnostic utility of MPI for ischemic LV dysfunction in new-onset HF and sets the stage for a prospective randomized study to confirm these findings.
INDICATIONS AND USAGE FOR CARDIOLITE®:
Indications and Usage Cardiolite®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, is a myocardial perfusion agent that is indicated for detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects), in evaluating myocardial function and developing information for use in patient management decisions. Cardiolite® evaluation of myocardial ischemia can be accomplished with rest and cardiovascular stress techniques (e.g., exercise or pharmacologic stress in accordance with the pharmacologic stress agent’s labeling).

It is usually not possible to determine the age of a myocardial infarction or to differentiate a recent myocardial infarction from ischemia.

IMPORTANT SAFETY INFORMATION FOR CARDIOLITE:
Exercise and pharmacologic stress testing should be performed only under the supervision of a qualified physician. Cardiolite® has been rarely associated with acute severe allergic events of angioedema and urticaria. The most frequently reported adverse events include headache, chest pain/angina, ST segment changes on ECG, nausea, and abnormal taste and smell.
CARDIOLITE® Kit for the Preparation of Technetium Tc99m Sestamibi for Injection

FOR DIAGNOSTIC USE

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CARDIOLITE® safely and effectively. See full prescribing information for CARDIOLITE®
CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection. Initial U.S. Approval: December, 1990

RECENT MAJOR CHANGES
Use in specific populations (8.3)

10/2007

INDICATIONS AND USAGE
CARDIOLITE® is a myocardial perfusion agent indicated for:
- detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects), in evaluating myocardial function and developing information for use in patient management decisions

DOSE AND ADMINISTRATION
For Myocardial Imaging:
The suggested dose range for IV administration of CARDIOLITE® is 370 - 1110 MBq (10 - 30 mCi).

For Breast Imaging:
The recommended dose range for IV administration of MIRALUMA® is a single dose of 740 - 1110 MBq (20 - 30 mCi).

DOSE FORMS AND STRENGTHS
CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection is supplied as a lyophilized mixture in a 5 ml vial.

CONTRAINDICATIONS
None known

WARNINGS AND PRECAUTIONS
- Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, and death, particularly in diabetic events.

CARDIOLITE® has not been studied in patients with sepsis, glandular enteritis, or acute inflammatory conditions.

- CARDIOLITE® has been rarely associated with acute severe allergic and anaphylactic reactions.

- CARDIOLITE® is contraindicated in patients with known allergy to the Technetium 99m compound. Be alert to the possibility of allergic reactions to either drug.

- The contents of the vial are not intended 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.

ADVERSE REACTIONS
- The following adverse reactions have been reported in ≥ 0.1% of patients: signs and symptoms consistent with stress occurring shortly after administration of the agent; transient arboritis, angina, arrhythmias, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, ashen, and vomiting within two hours after a second injection of Technetium Tc99m Sestamibi. A few cases of flushing, edema, injection site inflammation, dizziness, fever, pruritis, rash, urticaria and fatigue have also been attributed to administration of the agent.

To report SUSPECTED ADVERSE REACTIONS, contact Lantheus Medical Imaging, Inc. at 1-800-362-0668 or FDA at 1-800-FDA-1088 or 1-800-332-1088 (TTY: 1-800-311-0887)

DRUG INTERACTIONS
Specific drug-drug interactions have not been studied.

USE IN SPECIFIC POPULATIONS
In one study of 46 subjects who received CARDIOLITE® administration, the radioactivity in both children and adolescents exhibited blood PK profiles similar to those previously reported in adults.

See 17 FOR PATIENT COUNSELING INFORMATION

Table 1.0. Radiation Absorbed Doses from Tc99m Sestamibi

<table>
<thead>
<tr>
<th>Organ</th>
<th>30 mCi</th>
<th>1110 MBq</th>
<th>30 mCi</th>
<th>1110 MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial doses to organs and tissues of an average patient (70 kg) per dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breasts</strong></td>
<td>2.0</td>
<td>2.0</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.0</td>
<td>2.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>4.0</td>
<td>4.2</td>
<td>6.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Liver</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Ovaries</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Testes</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>2.0</td>
<td>2.0</td>
<td>4.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Total Body</td>
<td>0.5</td>
<td>0.5</td>
<td>4.8</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Radionuclide dosimetry calculations performed by Radiation Internal Dose Information Center, Oak Ridge Institute for Science and Education, PO Box 117, Oak Ridge, TN 37831-0117.

2.3 Instructions For Preparation
Preparation of the Technetium Tc99m Sestamibi from the Kit for the Preparation of Technetium Tc99m Sestamibi is done by the following aseptic procedure:

General 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 if found. Tear off a radial 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.

Boiling Water Bath Procedure:
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 [825 - 5500 MBq, (25 - 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 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 clip.

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

Resen-o-Stat (thermal cyclic) Procedure:
c. Place the vial in the thermal cyclic radiation shield.

d. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection [825 - 5500 MBq, (25 - 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. Place shield on sample block. While slightly pressing downward, give the shield a quarter turn to make certain there is a firm fit between the shield and the sample block.

h. Press the proceed button to initiate the program (the thermal cyclic automatically heats & cools the vial and contents). Please see the Resen-o-Stat Instruction Manual for further details.

General Procedure (cont.):
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 Tc99m concentration, total volume, assay time and date, expiration time and lot number on the vial label and affix the label to the shield.

k. Store the reaction vial containing the Technetium Tc99m Sestamibi at 15° to 25°C (59-77°F) until used; at such time the product should be aseptically withdrawn. Technetium Tc99m Sestamibi should be used within six hours following preparation. The vial contains no preservative.

Note: Adherence to the above product recertification instructions is recommended. The potential for cracking and significant contamination exists whenever vials containing radioactive material are heated. Product should be used within 6 hours after preparation. Final product with radiochemical purity of at least 90% was used in the clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method.
Radioisotopes should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose training and experience have been approved by the appropriate government agency authorized to license the use of radionuclides.

Stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support equipment.

The most frequent exercise stress test endpoints sufficient to stop the test reported during controlled studies (two-thirds were cardiac patients) were:

- Fatigue 35%
- Dyspnea 17%
- Chest Pain 16%
- Light-headedness/t-Depression 16%
- Arthrythmia 1%

6. ADVERSE 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 women’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 (see Section 5). Adverse events reported at a rate of 0.5% or greater after receiving Technetium Tc99m Sestamibi administration are shown in the following tables.

### Table 2.0

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1%</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1%</td>
</tr>
<tr>
<td>Rash</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1%</td>
</tr>
<tr>
<td>Arthrythmia</td>
<td>1%</td>
</tr>
</tbody>
</table>

7. DRUG INTERACTIONS

Specific drug-drug interactions have not been studied.

8. USE IN SPECIFIC PATIENTS

8.1 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.

8.3 Nursing Mothers

Technetium Tc99m Sestamibi is excreted in human milk during lactation. It is not known whether Technetium Tc99m Sestamibi is excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established. No evidence of diagnostic efficacy or clinical utility of CARDIOLITE® scan was found in clinical studies of children and adolescents with Kawasaki disease.

A prospective study of 445 pediatric patients with Kawasaki disease was designed to determine the predictive value of CARDIOLITE® rest and stress myocardial perfusion imaging in defining a pediatric population with Kawasaki disease that was at risk of developing cardiac events. Cardiac events were defined as cardiac death, MI, hospitalization due to cardiac etiology, heart failure, CABG or coronary angioplasty. The standard of truth was defined as cardiac events occurring 6 months following the administration of CARDIOLITE®. Only three cardiac events were observed at six months in this study. In all three cases, the scan was negative. No clinically meaningful measurements of sensitivity, specificity or other diagnostic performance parameters could be demonstrated in this study.

### Table 3.0. Principal Radiation Emission Data

<table>
<thead>
<tr>
<th>Emission Type</th>
<th>Mean %</th>
<th>Mean Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gamma rays</td>
<td>98.9%</td>
<td>140 keV</td>
</tr>
</tbody>
</table>

8.5 Geriatric Use

Of 3068 patients in clinical studies of CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, 693 patients were 65 or older and 121 were 75 or older.

Of 673 patients in clinical studies of MIRALYM®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, 138 patients were 65 or older and 30 were 75 or older.

On the basis of the evaluation of the frequency and adverse events and review of vital signs data, no overall differences in safety were observed between these subjects and younger subjects. Although reported clinical experience has not identified differences in response between elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

9. DRUG ABUSE AND DEPENDENCE

No abuse. No dependence.

10. OVERDOSAGE

The clinical consequences of overdosing with CARDIOLITE® are not known.

11. DESCRIPTION

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

- Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0 mg
- Sodium Citrate Dihydrate - 2.6 mg
- L-Cysteine Hydrochloride Monohydrate - 1.0 mg
- Sodium Chloride - 10 mg
- Stannous Chloride, Dihydrate, minimum (SnCl2·2H2O) - 0.025 mg
- Stannous Chloride, Dihydrate, maximum (SnCl2·2H2O) - 0.075 mg
- Stannous chloride (stannous stannic) Dihydrate, maximum (as SnCl2·2H2O) - 0.086 mg

Prior to lyophilization the pH is 3.5 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 solution. The pH of the reconstituted product is 5.5 (3.0 – 6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is Tc99m(MIBI)3+, where MIBI is 2-methoxy isobutyl isonitrile.

11.1 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 below in Table 4.0.

### Table 4.0. Radionuclide Emission Data

<table>
<thead>
<tr>
<th>Emission Type</th>
<th>Mean %</th>
<th>Mean Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gamma rays</td>
<td>98.9%</td>
<td>140 keV</td>
</tr>
</tbody>
</table>


11.2 External Radiation

The specific gamma ray constant for Tc99m is 5.4 microcuries/mg-keV-hr at 1 cm. The first half value layer is 0.017 cm of Pt. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interaction of various thicknesses of Pt is shown in Table 4.0. To calculate the rate of radiation exposure from MegaBecquerel (microlitre) units of this radionuclide, the amount of a 0.25 cm thickness of Pt will attenuate the radiation emitted by a factor of 1.000.

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 5.0.

12. CLINICAL PHARMACOLOGY

12.1 Tissue Uptake

In a clinical pharmacology study, 46 pediatric patients with Kawasaki disease received CARDIOLITE® administration at the following doses: 0.1 - 0.2 mCi/kg for rest, 0.3 mCi/kg for stress in one day studies; 0.2 mCi/kg for rest and 0.2 mCi/kg for stress in two day studies.

The radioactivity both in younger children and in adolescents exhibited PK profiles similar to those previously reported in adults (See Section 12). The radiation absorbed doses in adolescents, both at rest and stress, were similar to those observed in adults (see Section 2). When comparing weight-adjusted radioactivity (up to 0.3 mCi/kg) doses administered to adolescents and younger children to the recommended dose administered to adults (up to 0.3 mCi/kg), the radiation absorbed doses in both adolescents and younger children were similar to those in adults.

Adverse events were evaluated in 609 pediatric patients from the three clinical studies described above. The frequency and the type of the adverse events were similar to those the ones observed in the studies of CARDIOLITE® in adults. Two of the 609 had a serious adverse event: one patient received a CARDIOLITE® overdose but remained asymptomatic, and one patient had an asthma exacerbation following administration.

13. PRECAUTIONS

None known.

14. WARNINGS AND PRECAUTIONS

5.1 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 accepted clinical procedure. If adverse events occur 24 to 48 hours after Technetium Tc99m Sestamibi use and is usually associated with exercise stress testing (See Section 5.2).

Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction and cerebrovascular events.

Caution should be used when pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the pharmacologic stress agent's labeling.

Technetium Tc99m Sestamibi has been rarely associated with acute severe allergic and anaphylactic events of angioedema and generalized urticaria. In some patients the allergic symptoms developed on the second injection during CARDIOLITE® imaging. Patients who receive CARDIOLITE® or MIRALYM® imaging are receiving the same drug.

Caution should be exercised and emergency equipment should be available when administering Technetium Tc99m Sestamibi. Also, before administering either CARDIOLITE® or MIRALYM®, patients should be asked about the possibility of allergic reactions to either drug.

5.2 General Precautions

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.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to the patients consistent with proper patient management.

Contents of the kit before preparation are not radioactive. However, after the Sodium Pertechnetate Tc99m Injection 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 Tc99m labelling reactions depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m injection containing oxidants should not be used.

Technetium Tc99m Sestamibi should not be used more than six hours after preparation.
Table 8.0. Physical Decay Chart; Tc99m Half-Life 6.02 Hours

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Hours Remaining</th>
<th>Remaining</th>
<th>Hours Remaining</th>
<th>Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0⁺</td>
<td>1,000</td>
<td>8</td>
<td>39.8</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8991</td>
<td>9</td>
<td>35.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7794</td>
<td>10</td>
<td>31.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7018</td>
<td>11</td>
<td>28.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5563</td>
<td>12</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4001</td>
<td>13</td>
<td>20.1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>311</td>
<td>14</td>
<td>16.2</td>
<td></td>
</tr>
</tbody>
</table>

*Calibration

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Technetium Tc99m Sestamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in a manner analogous to that of thallous chloride Tl-201. Scintigraphic images obtained in humans after the intravenous administration of the drug have been comparable to those obtained with thallous chloride Tl-201 in normal and abnormal myocardial tissue.

Animal studies have shown that myocardial uptake is not blocked when the sodium pump mechanism is inhibited. Although studies of subcellular fractionation and electron micrographic analysis of heart cell aggregates suggest that Tc99m Sestamibi cellular retention occurs specifically within the mitochondria as a result of electrostatic interactions, the clinical relevance of these findings has not been determined.

The mechanism of Tc99m Sestamibi localization in various types of breast tissue (e.g., benign, inflammatory, malignant, fibrous) has not been established.

12.3 Pharmacokinetics
Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast component clears with a t½ of 4.4 to 4.3 minutes at rest, and clears with a t½ 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 Tc99m Sestamibi in plasma.

The biological half-life is approximately six hours after a rest or exercise injection. The biological half-life for the liver is approximately 30 minutes after a rest or exercise injection. The effective half-life of clearance (which includes both the biological half-life and radionuclide decay) for the heart is approximately 3 hours, and for the liver is approximately 30 minutes, after a rest or exercise injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake.

Myocardial uptake which is coronary flow dependent is 1.2% of the injected dose at rest and 1.5% of the injected dose at exercise. Table 6.0 illustrates the biological clearance as well as effective clearance (which includes biological clearance and radionuclide decay) of Tc99m Sestamibi from the heart and liver.

<p>| Organ [concentrations expressed as percentage of injected dose; data based on an average of 5 subjects at rest and 5 subjects during exercise] |</p>
<table>
<thead>
<tr>
<th>Heart</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min.</td>
<td>1.2</td>
</tr>
<tr>
<td>10 min.</td>
<td>1.0</td>
</tr>
<tr>
<td>30 min.</td>
<td>1.0</td>
</tr>
<tr>
<td>1 hour</td>
<td>1.0</td>
</tr>
<tr>
<td>2 hours</td>
<td>1.0</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.8</td>
</tr>
</tbody>
</table>

A study in a dog myocardial ischemia model reported that Technetium Tc99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than thallous chloride Tl-201. A study in a dog myocardial ischemia model reported that the dose showed no redistribution of any degree of MIRALUMA® uptake.

12.3.2 Elimination
The agent is excreted without any evidence of metabolism.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.5 mrad/30 mCi at rest, 1.2 rad/mCi at exercise) is high. Minimal exposure to female ALABAR (a group of women) is necessary in women of childbearing capability. (See Section 2.)

The active intermediate, CuMBI_BF₃ was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHL/HRP and intravenous administration tests (≥20 µg/ml). An increase in cells with chromosome aberrations was observed in the in vitro human lymphocyte assays. CuMBI_BF₃ 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 > 400 x maximal human dose).

14. CLINICAL STUDIES:
CLINICAL TRIALS:
Myocardial Imaging: In a trial of rest and stress CARDIOLITE® imaging, the relationship of normal or abnormal perfusion scans and long term cardiac events was evaluated in 521 patients (511 men, 10 women) with stable chest pain. There were 73.9% Caucasians, 25.9% Blacks and 0.2% Asians. The mean age was 59.6 years (range: 29 to 84 years). All patients had a baseline rest and exercise CARDIOLITE® scan and were followed for 12.2 ± 4.9 months (range: 1 to 24 months). Images were correlated with the occurrence of a cardiac event (cardiac death or non-fatal myocardial infarction). In this trial as summarized in Table 7.0, 24/21 (4.6%) had a cardiac event.

<table>
<thead>
<tr>
<th>Table 7.0 Cardiac Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Scan²⁺</td>
</tr>
<tr>
<td>Normal:</td>
</tr>
<tr>
<td>Abnormal:</td>
</tr>
</tbody>
</table>

*Note: Similar findings were found in two studies with patients who had pharmacologic stress CARDIOLITE® imaging.

Table 6.0. Biological and Effective Clearance

<table>
<thead>
<tr>
<th>REST</th>
<th>STRESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological</td>
<td>Effective</td>
</tr>
<tr>
<td>5 min.</td>
<td>1.2</td>
</tr>
<tr>
<td>10 min.</td>
<td>1.0</td>
</tr>
<tr>
<td>30 min.</td>
<td>1.0</td>
</tr>
<tr>
<td>1 hour</td>
<td>1.0</td>
</tr>
<tr>
<td>2 hours</td>
<td>1.0</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.8</td>
</tr>
</tbody>
</table>

A study in a dog myocardial ischemia model reported that Technetium Tc99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than thallous chloride Tl-201. A study in a dog myocardial ischemia model reported that the dose showed no redistribution of any degree of MIRALUMA® uptake. In these two studies approximately 150 additional, non-biopsied lesions were found to be positive after MIRALUMA® imaging. These lesions were identified in sites that did not physically correlate with identified entry criteria mammographic lesions and these lesions were not palpable. These lesions were not biopsied. When these lesions were benign or malignant disease was not known. MIRALUMA® uptake can occur in both benign and malignant disease. THE CLINICAL USEFULNESS OF A POSITIVE MIRALUMA® IMAGE IN THE ABSENCE OF AN ABNORMAL MAMMORAM OR ABNORMAL LESION IS NOT KNOWN.

15. REFERENCES
Not applicable.

16. HOW SUPPLIED/STORAGE AND HANDLING
CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection is supplied as a 5 mL vial in kits of five (5) vials (NDC # 11994-001-05) and twenty (20) vials (NDC # 11994-001-20), sterile and non-pyrogenic.

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

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

Prior to lyophilization the pH is between 5.3-5.9. The contents of the vial are sterilized and stored under nitrogen. Store at 15 to 25°C (59-77°F) before and after reconstitution.

Technetium Tc99m Sestamibi contains no preservatives. Included in each five (5) vial kit is one (1) package insert, six (6) vial shield labels and six (6) radiation warning labels. Included in each twenty (20) vial kit is one (1) package insert, twenty four (24) vial shield labels and twenty four (24) radiation warning labels. This reagent kit is approved for distribution to persons licensed pursuant to the Code of Massachusetts Regulations 105 CMR 120.500 for the users listed in 105 CMR 120.547 or 120.552, or under equivalent regulations of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States.

17. PATIENT COUNSELING INFORMATION
CARDIOLITE® and MIRALUMA® are different names for the same drug. Patients should be advised to inform their health care provider if they had an allergic reaction to either drug or if they had an imaging study with either drug.