2017 Medicare Nuclear Medicine
Reimbursement Information
If you have questions regarding reimbursement for Lantheus Medical Imaging products, call Randy VanCoughnett at 978-436-7995 or email randy.vancoughnett@lantheus.com.

**CPT® – Current Procedural Terminology**

- American Medical Association’s five digit numeric codes used to report medical procedures and services.

**HCPCS - Healthcare Common Procedure Coding System**

- Level II HCPCS codes alphanumeric five digit codes primarily to identify contrast agents, radiopharmaceuticals, supplies and devices.

**Q-codes**

- Temporary codes created by Medicare to identify items not assigned a CPT code. Many drugs, supplies and biologicals are assigned Q codes.

**NDC codes – National Drug Code**

- A unique numeric code to identify drugs. The first segment of numbers identifies the labeler or manufacturer, the second segment identifies the product, and the third identifies the package.

**HOPPS – Hospital Outpatient Prospective Payment System**

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Three Basic Components of Reimbursement: Coding, Coverage and Payment.

1. Coding: There must be a CPT code or HCPCS code that accurately describes the service performed and/or the drugs provided.

2. Coverage: The existence of CPT and/or HCPCS codes used to report the services performed or items furnished does not guarantee coverage.

Medicare only covers a procedure, drug or supply when it is medically necessary. Providers should obtain and follow the policies and guidelines published by Medicare in the Local and National Coverage Determinations.

3. Payment: If the proper codes exist and there is coverage established, Medicare must set a payment amount for the drugs, supplies and/or procedures in order for providers to receive payment. Most payment amounts are determined by CMS nationally. There are differences in procedure payment amounts from region to region to reflect geographic differences in provider costs.

Documentation: When radiopharmaceuticals or contrast agents are reported, providers must document in the medical record the name of the drug and the amount administered.

Lantheus Medical Imaging cannot guarantee coverage or payment for products or procedures. Payer policies can vary widely. For more specific information, contact the payer directly in order to obtain up to date coverage, coding and payment information.
2017 Medicare Reimbursement Information Lantheus Medical Imaging

2017 Medicare Reimbursement for Nuclear Medicine
Non-HEU Derived Tc-99m for Medicare Hospital Outpatients\textsuperscript{1,2}

For 2017, CMS will continue the $10 add-on payment for non-HEU derived Tc-99m for hospital outpatients.

The United States government has established an agenda to eliminate domestic reliance on Tc-99m derived from nuclear reactors using Highly Enriched Uranium (HEU). CMS recognizes that Tc-99m derived from a non-HEU source may have a higher cost. In response, CMS will reimburse providers $10 per non-HEU derived Tc-99m dose in the hospital outpatient setting in addition to the payment for the imaging procedure.

Under this policy, hospitals report HCPCS code Q9969 (Tc-99m from non-highly enriched uranium source, full cost recovery add-on, per study dose) once per dose along with any diagnostic scan or scans furnished using Tc-99m as long as the Tc-99m doses used can be certified by the hospital to be at least 95 percent derived from non-HEU sources.

1. CMS created HCPCS code Q9969 to report non-HEU Tc-99m doses.

   **HCPCS Descriptor**

   *Q9969 Tc-99m from non-highly enriched uranium source, full cost recovery add-on, per study dose*

2. CMS will reimburse $10 per dose for Q9969 in addition to the imaging procedure.

3. Hospital reports token $1 charge per dose for Q9969.

Hospitals do not indicate a dose is from a non-HEU source on their claim form. They simply report HCPCS Q9969 for each non-HEU dose. If asked, a hospital has three options to document a dose was derived from a non-HEU source\textsuperscript{2}.

1. Produce invoices, patient dose labels or tracking sheets that indicate that a dose was produced from non-HEU sources.

2. Produce documentation that an entire batch of Tc-99m doses were derived from a non-HEU source for a specified period of time that a single non-HEU generator was in use or manufacturer attestation that a generator is non-HEU generator.

3. If the manufacturer has labeled a generator or a dose attesting to it being derived from a non-HEU source.

If a hospital has any questions about whether they are receiving Tc-99m derived from a non-HEU source, they should contact their radiopharmacy or the generator manufacturer.

For more information, please see Federal Register / Vol. 78, No. 237 / Tuesday, December 10, 2013 p.75002-75003 or Federal Register / Vol. 77, No. 221 / Thursday, November 15, 2012 / p. 68316-68317 or contact your local radiopharmacy or your Tc-99m generator manufacturer.
Medicare Hospital Outpatient

For 2017, CMS continues to package the payment for the exercise stress test, CPT 93017, and all pharmacologic stress agents with the SPECT Myocardial Perfusion Imaging (MPI) procedure, CPT 78452, into a single payment. The exercise test, radiopharmaceutical and pharmacologic stress agent are not paid separately.

If a non-HEU derived Tc-99m dose is used, providers will receive a separate add on payment of $10 per dose by reporting HCPCS code Q9969.

**Packaged components of SPECT Multiple Myocardial Perfusion CPT 78452**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>2017</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>78452 SPECT MPI multiple</td>
<td>$1138.46</td>
<td>$1,108.46</td>
</tr>
<tr>
<td>93017 Exercise test packaged with 78452</td>
<td>$0 packaged with 78452</td>
<td>$0 packaged with 78452</td>
</tr>
<tr>
<td>Jxxxx Pharmacologic stress agent</td>
<td>$0 packaged with 78452</td>
<td>$0 packaged with 78452</td>
</tr>
<tr>
<td>A95000 Tc-99m sestamibi</td>
<td>$0 packaged with 78452</td>
<td>$0 packaged with 78452</td>
</tr>
<tr>
<td>Q9969 Tc-99m non-HEU source per dose</td>
<td>$10 paid separately</td>
<td>$10 paid separately</td>
</tr>
</tbody>
</table>

**Selected 2017 payment* Medicare Hospital Outpatients and Physician Office**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Descriptor</th>
<th>Hospital APC</th>
<th>Hospital Outpatient Payment</th>
<th>Global Physician Office Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>78071</td>
<td>Parathyroid planar imaging (including subtraction, when performed); with tomographic (SPECT)</td>
<td>5591</td>
<td>$332.94</td>
<td>$375.04</td>
</tr>
<tr>
<td>78452</td>
<td>Myocardial Perfusion imaging multiple SPECT</td>
<td>5593</td>
<td>$1,138.46</td>
<td>$494.55*</td>
</tr>
<tr>
<td>78582</td>
<td>Pulmonary ventilation (e.g. aerosol or gas) and perfusion imaging</td>
<td>5592</td>
<td>$428.95</td>
<td>$351.35</td>
</tr>
<tr>
<td>78607</td>
<td>Brain imaging tomographic (SPECT)</td>
<td>5593</td>
<td>$1138.46</td>
<td>$368.94</td>
</tr>
<tr>
<td>78806</td>
<td>Radiopharmaceutical localization of inflammatory process; whole body</td>
<td>5593</td>
<td>$1138.46</td>
<td>$349.91</td>
</tr>
<tr>
<td>79101</td>
<td>Radiopharmaceutical therapy, by intravenous administration</td>
<td>5661</td>
<td>$216.59</td>
<td>$146.78</td>
</tr>
</tbody>
</table>

Physician Payment amounts as of January 1, 2017. National average payments based on Medicare Conversion factor of $35.8887 and January 2017 Medicare Addendum B relative value units*.

*Radiopharmaceutical, exercise test and pharmacologic stress agent all paid separately for physician office.
Lantheus Medical Imaging 2017 HCPCS and NDC Information

QUADRAMET® HCPCS code A9604 - NDC 11994-016-01
Samarium 153 lexidronam therapeutic, per treatment dose, up to 150 millicuries.

Medicare Hospital Outpatients

- QUADRAMET®- Therapeutic radiopharmaceuticals reimbursed at 106% of ASP-payment updated quarterly.
- Latest payment amount can be seen at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates.html

Medicare non hospital physician offices / IDTFs

- QUADRAMET®- Reimbursement based on AWP or invoice.
- Check with local Medicare MAC for local payment amount.

<table>
<thead>
<tr>
<th>Product</th>
<th>HCPCS</th>
<th>All diagnostic radiopharmaceutical payments are packaged in HOPPS. Part B payment is based on AWP or invoice.</th>
</tr>
</thead>
</table>
| Cardiolite® Kit for the Preparation of Technetium Tc-99m Sestamibi for Injection | A9500 | • NDC 11994-001-20  
• NDC 11994-001-52  
• NDC 11994-001-55 |
| Thallous Chloride Thallium 201 Injection                                 | A9505 | • NDC 11994-427-11  
• NDC 11994-427-15  
• NDC 11994-427-19  
• NDC 11994-427-24  
• NDC 11994-427-26  
• NDC 11994-427-28 |
| Gallium Citrate Ga-67 Injection                                         | A9556 | • NDC 11994-121-06  
• NDC 11994-121-08  
• NDC 11994-121-13  
• NDC 11994-121-19 |
| NEUROLITE® Kit for the Preparation of Technetium Tc-99m Bicisate for Injection | A9557 | • NDC 11994-006-02  
• NDC 11994-006-05 |
| Xenon Xe-133 Gas                                                       | A9558 | • NDC 11994-127-11  
• NDC 11994-127-15  
• NDC 11994-127-21  
• NDC 11994-127-25 |
| Tc-99m from non-highly enriched uranium source, full cost recovery add-on, per study dose | Q9969 | • Paid $10 per dose for Tc-99m doses derived from \( \geq 95\% \) non-HEU for HOPPS in addition to APC payment for imaging procedure  
• $10 add on payment not paid in office setting |
Citations


2. Federal Register / Vol. 77, No. 221 / Thursday, November 15, 2012 68316


NDC codes can be researched at http://www.accessdata.fda.gov/scripts/cder/ndc/
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)

INDICATIONS AND USAGE

CARDIOLITE® is a myocardial perfusion agent indicated for:

• detecting/coronyary 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

—DOSEAGE AND ADMINISTRATION

• For Myocardial Imaging: The suggested dose range for IV administration of CARDIOLITE® in a single dose to be employed in the average patient (70 Kg) 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).

—DOSEAGE 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, thrombocytopenia and cerebrovascular events.

• CARDIOLITE® has been rarely associated with severe allergic and anaphylactic events of angioedema and generalized urticaria. In some patients the allergic symptoms developed on the second injection during CARDIOLITE® imaging.

• Caution should be exercised and emergency equipment should be available when administering CARDIOLITE®

• Before administering CARDIOLITE®, patients should be debriefed about the possibility of allergic reactions to either drug.

• 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 preparation procedure.

—ADVERSE REACTIONS

• The following adverse reactions have been reported in > 0.5% of patients: signs and symptoms consistent with those occurring shortly after administration of the agent; transient arteritis, angioedema, arrhythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthma, and vomiting occurring within two hours after a second injection of Technetium Tc99m Sestamibi. A few cases of flushing, edema, injection site inflammation, deep, mouth, pruritis, rash, urticaria and fatigue have also been attributed to administration of the agent.

To report SUSPECTED ADVERSE REACTIONS, contact Lanthane Medical Imaging, Inc. at 1-800-382-2668 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

—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

Revised: May 2014

FULL PRESCRIBING INFORMATION: CONTENTS:

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2.2 Radiation Dosimetry
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2.4 Determination of Radiochemical Purity in Technetium Tc99m Sestamibi
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
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6. ADVERSE REACTIONS
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*Sections or subsections omitted from the full prescribing information are not listed.

1. INDICATIONS AND USAGE

Myocardial Imaging: 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.

Breast Imaging: MIRALUMA®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, is indicated for planar imaging as a second line diagnostic agent to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass.

MIRALUMA® is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy.

2. DOSAGE AND ADMINISTRATION

For Myocardial Imaging: The suggested dose range for IV administration of CARDIOLITE® in a single dose to be employed in the average patient (70 Kg) 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).

2.1 Image Acquisition

Breast Imaging: It is recommended that images are obtained with a table overlay. For anterior images, position the patient supine with both arms behind the head, chest and abdomen against the table, head turned to the side and relaxed, with the breast imaged from the patient prone with the isolateral arm comfortably above the head, shoulders flat against the table, head turned to the side and relaxed, with the breast imaged overlay. For lateral images, position the patient prone with the isolateral arm comfortably above the head, shoulders flat against the table, head turned to the side and relaxed, with the breast imaged from the patient prone with the isolateral arm comfortably above the head, shoulders flat against the table, head turned to the side and relaxed, with the breast imaged.

2.2 Radiation Dosimetry

The radiation doses to organs and tissues of an average patient (70 Kg) per 2.0 hour void and 4.8 hour void are as follows:

<table>
<thead>
<tr>
<th>Organ</th>
<th>2.0 hour void</th>
<th>4.8 hour void</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mGy/MBq</td>
<td>mGy/MBq</td>
</tr>
<tr>
<td>Breast</td>
<td>0.2 - 2.0</td>
<td>0.2 - 1.9</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.0 - 20.0</td>
<td>2.0 - 20.0</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>3.0 - 30.0</td>
<td>3.0 - 30.0</td>
</tr>
<tr>
<td>Upper Large Intestine</td>
<td>5.4 - 55.5</td>
<td>5.4 - 55.5</td>
</tr>
<tr>
<td>Wall</td>
<td>3.9 - 40.0</td>
<td>4.2 - 41.1</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>0.6 - 6.1</td>
<td>0.6 - 5.8</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.5 - 5.1</td>
<td>0.5 - 4.9</td>
</tr>
<tr>
<td>Kidneys</td>
<td>2.0 - 20.0</td>
<td>2.0 - 20.0</td>
</tr>
<tr>
<td>Liver</td>
<td>0.6 - 5.8</td>
<td>0.6 - 5.7</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.3 - 2.8</td>
<td>0.3 - 2.7</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>0.7 - 6.8</td>
<td>0.7 - 6.4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.7 - 7.0</td>
<td>0.7 - 7.0</td>
</tr>
<tr>
<td>Ovaries</td>
<td>1.5 - 15.5</td>
<td>1.5 - 15.5</td>
</tr>
<tr>
<td>Testes</td>
<td>0.3 - 3.4</td>
<td>0.4 - 3.9</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.5 - 4.6</td>
<td>0.5 - 4.4</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>2.0 - 20.0</td>
<td>2.0 - 41.1</td>
</tr>
<tr>
<td>Total Body</td>
<td>0.5 - 4.8</td>
<td>0.5 - 4.8</td>
</tr>
</tbody>
</table>
Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training 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%
- Angina pectoris/T-depression 10%
- Arthralgia 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 patients’ genders were not recorded) were in cardiac clinical trials and 673 (100%) women in breast imaging trials. Cases of angina, chest pain, and death have occurred (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 table.

Table 2.0

<table>
<thead>
<tr>
<th>Body System</th>
<th>Cardiac Symptoms</th>
<th>Cardiac Events</th>
<th>Other Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women n = 673</td>
<td>Men n = 685</td>
<td>Men n = 2361</td>
<td>Total n = 3040</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>21 (3.1%)</td>
<td>6 (0.9%)</td>
<td>17 (0.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (2.3%)</td>
<td>2 (0.3%)</td>
<td>11 (0.4%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>9 (1.3%)</td>
<td>24 (3.5%)</td>
<td>75 (3.2%)</td>
</tr>
<tr>
<td>Chest Pain/Anosmia</td>
<td>0 (0%)</td>
<td>18 (2.6%)</td>
<td>46 (1.8%)</td>
</tr>
<tr>
<td>SI segment changes</td>
<td>0 (0%)</td>
<td>11 (1.6%)</td>
<td>29 (1.2%)</td>
</tr>
<tr>
<td>Diastolic System</td>
<td>8 (1.2%)</td>
<td>4 (0.6%)</td>
<td>9 (0.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (0.6%)</td>
<td>1 (0.1%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Special Senses</td>
<td>132 (19.0%)</td>
<td>62 (9.1%)</td>
<td>160 (6.8%)</td>
</tr>
<tr>
<td>Taste Perversion</td>
<td>129 (19.2%)</td>
<td>60 (8.8%)</td>
<td>157 (6.8%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8 (1.2%)</td>
<td>6 (0.9%)</td>
<td>10 (0.4%)</td>
</tr>
<tr>
<td>Excludes 22 patients whose gender was not recorded</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 at a rate of 0.5% of patients: signs and symptoms consistent with severe occurring shortly after administration of the agent, e.g., tachycardia, angina, arrhythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthma, and vomiting within two hours after a second injection of the agent (see Section 5.2.1). A few cases of flushing, edema, injection site inflammation, dry mouth, fever, pruritis, rash, urticaria and fatigue have also been attributed to administration of the agent.

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. Therefore, formula feedings should be substituted for breast feedings.

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 to define 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, CAGB 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.

A ten-year retrospective case history study of pediatric Kawasaki disease patients who completed CARDIOLITE myocardial perfusion imaging and who had coronary angiography within three months of the CAROLITE scan was designed to measure sensitivity and specificity of CARDIOLITE scan. Out of 72 patients who had both evaluable CARDIOLITE scans and evaluable angiographic images, only one patient had both an abnormal angiogram and an abnormal CARDIOLITE scan. No clinically meaningful measurements of sensitivity, specificity or other diagnostic performance parameters could be demonstrated in this study.

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 (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 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.

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 MIRALUMA, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, 138 patients were 65 or older and 30 were 75 or older.

Based on the evaluation of the frequency of 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

9.1 Controlled Substance

Not applicable.

9.2 Abuse

Not applicable.

9.3 Dependence

Not applicable.

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 Dihydate - 2.6 mg
- L-Cysteine Hydrochloride Monohydrate - 1.0 mg
- Sodium Chloride - 60 mg
- Stannous Chloride, Dihydate, minimum (SnCl2+2H2O) - 0.025 mg
- Stannous Chloride, Dihydate, (SnCl3+2H2O) - 0.075 mg
- Chloride (stannous and stannic) Dihydate, maximum (as SnCl2+2H2O) - 0.086 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 Solution. 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)2, 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 hours1. Photos that are useful for detection and imaging studies are listed below in Table 3.0.

Table 3.0. Principal Radiation Emission Data

<table>
<thead>
<tr>
<th>Energy (KeV)</th>
<th>% Disintegration</th>
<th>Mean</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>140.3</td>
<td>89.0</td>
<td>0.075</td>
<td>0.08</td>
</tr>
<tr>
<td>128.0</td>
<td>10.0</td>
<td>0.016</td>
<td>0.025</td>
</tr>
<tr>
<td>112.0</td>
<td>10.0</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>


11.2 External Radiation

The specific gamma ray constant for Tc99m is 5.4 microcuries/kg-MBq/hr (0.798 R/mCi-hr) at 1 cm. The first half value layer is 0.017 cm of Pb. The contents of the vial are lyophilized and stored under nitrogen.

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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 is present with a t1/2a of 4.3 minutes at rest, and clears with a t1/2b 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 radiodecay) 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 radiodecay) of Tc99m Sestamibi from the heart and liver.

(a) Concentrations expressed as percentage of injected dose; data based on an average of 5 subjects at rest and 5 subjects during exercise.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Heart</th>
<th>Liver</th>
<th>Rest (80% biological half-life)</th>
<th>Effective (80% biological half-life)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.2</td>
<td>19.6</td>
<td>19.4</td>
<td>1.5</td>
</tr>
<tr>
<td>10</td>
<td>1.1</td>
<td>12.2</td>
<td>11.5</td>
<td>1.4</td>
</tr>
<tr>
<td>30</td>
<td>1.0</td>
<td>9.9</td>
<td>9.5</td>
<td>1.4</td>
</tr>
<tr>
<td>60</td>
<td>0.8</td>
<td>7.2</td>
<td>6.9</td>
<td>1.0</td>
</tr>
<tr>
<td>120</td>
<td>0.6</td>
<td>5.0</td>
<td>4.8</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. In a study in a dog myocardial infarction model reported that the drug showed no redistribution of any consequence. Definitive human studies to demonstrate possible redistribution have not been reported. In patients with documented myocardial infarction, imaging revealed the infarct up to 4 hours post dose.

12.3.1 Metabolism

The agent is excreted without any evidence of metabolism.

12.3.2 Elimination

The major pathway for clearance of Tc99m Sestamibi is the hepatobiliary system. Activity from the gall bladder 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.

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 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 Section 2.)

The active intermediate, Cu(MIBI)\(^{+}\), was found to genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HGPRT and SH-Muta sc vector exchange tests (\(>20 \times \text{BG}\)). An increase in cells with chromosome aberrations was observed in the in vivo human lymphocyte assay. Cu(MIBI)\(^{+}\) did not show genotoxic effects in the in vivo mouse micronucleus test at a dose which caused systemic and bone marrow toxicity (8 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 59.0 years (range: 29 to 84 years). All patients had a baseline rest and exercise CARDIOLITE\(^{®}\) scan and were followed for 13.2 ± 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, 24/26 (4.6%) had a cardiac event.

Table 8.0 Physical Decay Chart; Tc99m Half-Life 6.02 Hours

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Hours Remaining</th>
<th>Hours Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1,000</td>
<td>8</td>
</tr>
<tr>
<td>0.1</td>
<td>891</td>
<td>9</td>
</tr>
<tr>
<td>0.2</td>
<td>794</td>
<td>10</td>
</tr>
<tr>
<td>0.3</td>
<td>708</td>
<td>11</td>
</tr>
<tr>
<td>0.4</td>
<td>632</td>
<td>12</td>
</tr>
<tr>
<td>0.5</td>
<td>562</td>
<td>12</td>
</tr>
<tr>
<td>0.6</td>
<td>501</td>
<td>4.47</td>
</tr>
</tbody>
</table>

The decay curve is expressed in terms of half-life (T1/2) and disintegration constant (\(\lambda\)). The physical half-life is the time it takes for the radioactivity of a sample to decrease by a factor of two. The biological half-life is defined as the time required for the body to reduce the concentration of a substance by 50%.

<table>
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<tr>
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