CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection

Preparation of Technetium Tc99m Sestamibi from Sestamibi

General Procedure:

1. Add a sodium carrier to Technetium Tc99m Sestamibi. A few cases of flushing, edema, injection site striction and cerebrovascular events.

2. Dosage and Administration

2.1 Image Acquisition

Breast imaging: The radiation absorbed dose may be used in the average patient (70 KI) in 370 - 1110 MBq (10 - 30 mCi).

2.2 Radiation Dosimetry

The radiation absorbed dose of Technetium Tc99m Sestamibi is performed on the vial in the lead shield. The needle should be placed over the vial and connected to the radiation monitor. The radiation absorbed dose of Technetium Tc99m Sestamibi is shown in Table 1.0.

Table 1.0. Radiation Absorbed Doses from Tc99m Sestamibi

<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>rads/ mCi</td>
<td>rads/ mCi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breasts</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Upper Large Intestine</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Lower Large Intestine</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Kidneys</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Liver</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Ovaries</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Testes</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Total Body</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Note: Adherence to the above product reconstitution 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:

2.4 Determination of Radiochemical Purity in Technetium Tc99m Sestamibi

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 F, #2-cut to 2.5 cm x 7.0 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.

*Sections or subsections omitted from the full prescribing information are not listed.

- Adverse reactions such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction and cerebrovascular events.

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

- Breast imaging: The recommended dose range for I.V. administration of MIRALUMI® is a single dose of 740 - 1110 MBq (20 - 30 mCi).

- For Myocardial Imaging: The suggested dose range for I.V. administration of CARDIOLITE® is a single dose to be employed in the average patient (70 Kg) in 370 - 1110 MBq (10 - 30 mCi).

- For Breast Imaging: The recommended dose range for I.V. administration of MIRALUMI® is a single dose to be employed in the average patient (70 Kg) in 370 - 1110 MBq (10 - 30 mCi).

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

- These highlights do not include all the information needed to use CARDIOLITE® safely and effectively.

- The patient should be asked about the possibility of the patient being pregnant or nursing.

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6. ADVERSE REACTIONS

Adverse reactions were evaluated in 3741 adults who were evaluated in clinical studies. Of these, 3068 (79% 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. Cardiac 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 2.9

<table>
<thead>
<tr>
<th>Body System</th>
<th>Breast Studies</th>
<th>Cardiac Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11 (1.6%)</td>
<td>2.0 (0.2%)</td>
</tr>
<tr>
<td>Cardiac Pain/Anx</td>
<td>0 (0%)</td>
<td>18 (2.6%)</td>
</tr>
<tr>
<td>ST segment changes</td>
<td>0 (0%)</td>
<td>11 (1.6%)</td>
</tr>
<tr>
<td>Diastolic Systolic</td>
<td>8 (1.2%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (0.6%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Special Senses</td>
<td>132 (19.6%)</td>
<td>62 (9.1%)</td>
</tr>
<tr>
<td>Taste Paresthesia</td>
<td>129 (19.2%)</td>
<td>60 (8.8%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8 (1.2%)</td>
<td>6 (0.9%)</td>
</tr>
</tbody>
</table>

*Excludes the 22 patients whose gender was not recorded.

In the clinical studies for breast imaging, chest pain was reported in 12 (1.7%) of the patients; in 11 of these patients the pain appeared to be associated with biopsy/surgical procedures.

The following adverse reactions have been reported in 0.5% of patients: signs and symptoms consistent with severe occurring shortly after administration of the agent; transient arthritis, transient myositis, eosinophilia, anaphylaxis, dizziness, syncope, abdominal pain, vomiting, and severe hyperkalemia by diaphoresis, hypotension, bradycardia, chest pain, and vomiting within two hours after a second injection of Technetium Tc99m Sestamibi. A few cases of flushing, edema, injection site inflammatory response by face, fever, 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 POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with Technetium Tc99m Sestamibi use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse outcomes. Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Sestamibi. However, all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the significance of any potential fetal risk.

Risk Summary

Limited data in the scientific literature on the presence of Technetium Tc99m Sestamibi in human milk has demonstrated that 0.01% and 0.03% of maternal injected activity of Technetium Tc99m Sestamibi was excreted in human milk. Technetium Tc99m Sestamibi accumulates in the lactating breast (see Clinical Considerations). There are limited data in the scientific literature on effects of Technetium Tc99m Sestamibi on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s need for Technetium Tc99m Sestamibi and any potential adverse effects on the breastfeeding infant from Technetium Tc99m Sestamibi or from the underlying maternal condition.

Clinical Considerations

Interruption of breastfeeding after exposure to Technetium Tc99m Sestamibi is not necessary because Technetium Tc99m Sestamibi excretion in breast milk is low. However, a lactating woman may restrict close contact with her breast fed infant to a maximum of 5 hours in the 24 hour period after Technetium Tc99m Sestamibi administration in order to minimize radiolabel exposure.

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 retrospective case 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 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.

A ten year retrospective case study of pediatric Kawasaki disease patients who completed CARDIOLITE® myocardial perfusion imaging and who had coronary angiography within three months of the CARDIOLITE® 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 anatomic 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 study; 0.2 mCi/kg for rest and 0.2 mCi/kg for stress in two day studies.

The radioactivity both in younger and children 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 radiocurie (up to 0.3 mCi/kg) doses administered to adolescents and younger children to the recommended dose administered to adults (up to 30 mCi), 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 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. No one had an asthma exacerbation following administration.

8.5 Geriatric Use

Of 3086 patients in clinical studies of CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection is supplied as a lyophilized mixture in a 5 mL vial.

4. CONTRAINDICATIONS

None known.

5. WARNINGS AND PRECAUTIONS

5.1 Warnings

In studying patients in whom cardiac disease is known or suspected, care should be taken to assure correct monitoring and treatment in accordance with safe, accepted clinical procedure. Infrequently, death has occurred 4 to 24 hours after Tc99m Sestamibi administration. 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 effects of angioedema and generalized urticaria. In some patients the allergic symptoms developed on the second injection during CARDIOLITE® imaging. Patients who receive CARDIOLITE® or MIRALUMA® 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 MIRALUMA®, patients should be asked about the possibility of allergic reactions to either drug.

5.2 General Precautions

The contents of the vials 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 preparatory 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 Sestamibi labeling reactions depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m containing oxidants should not be used.

Technetium Tc99m Sestamibi should not be used more than six hours after preparation.

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 apparatus.

The most frequent stress test endpoints sufficient to stop the test reported during controlled studies (those three were cardiac patients were):

- Fatigue 35%
- Dyspnea 17%
- Chest Pain 16%
- ST depression 7%
- Arthralgia 1%
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 spin resonance of heart cell aggregates suggest that Tc-99m Sestamibi cardiac 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 Technetium Tc99m Sestamibi uptake in various types of perfusion tissue (e.g., ischemic, inflammatory, malignant, fibrinous) has not been established.

12.3 Pharmacokinetics

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast clearing component clears with a t½ of 4.3 minutes at rest, and with a t½ of 1.1 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 myocardial 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 radio- nucleide 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 radiotoxicity decay) of Tc-99m Sestamibi from the heart and liver.

<table>
<thead>
<tr>
<th>Type of Image</th>
<th>Scan Result</th>
<th>Proportion of N = 352 Malignant Lesions</th>
<th>Proportion of N = 298 Non-Malignant Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>N = 48</td>
<td>19 (41%)</td>
<td>29 (98%)</td>
</tr>
<tr>
<td>Normal</td>
<td>N = 298</td>
<td>20 (70%)</td>
<td>279 (97%)</td>
</tr>
</tbody>
</table>

An estimate of the likelihood of malignancy based on the MIRALUMA® uptake score in combination with the mammographic score has not been studied. 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. Whether these lesions were benign or malignant is not known. MIRALUMA® uptake can occur in both benign and malignant tissue. The clinical usefulness of a positive MIRALUMA® IMAGE in the ABSENCE of an ABDOMINAL MAMMAGRAPH or a PALPABLE LESION IS UNKNOWN.

12. CLINICAL PHARMACOLOGY

12.6 CLINICAL TRIALS:

12.6.1 Cardiac Events

Cardiac imaging, in a trial of rest and stress CAROLITE® imaging, the relationship of normal or abnormal perfusion scans and long term cardiac events was evaluated in 260 patients (110 women and 150 men). The mean age was 59 years (range: 29 to 84 years). All patients had a baseline rest and exercise CAROLITE® scan and were followed for 13.2 ± 4.9 months (range: 1 to 24 months) after correlation with the occurrence of a cardiac event (cardiac death or non-fatal myocardial infarction). In this trial as summarized in Table 7.0, 24/521 (4.6%) had a cardiac event.