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), and evaluating myocardial function and developing information for use in patient management decisions

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).

DOSE FORMS AND STRENGTHS

For diagnostic use.

CONTRAINDICATIONS

- None known

WARNING AND PRECAUTIONS

- Pharmacologic induction of cardiovascular stress may be associated with beginning five minutes after the injection of Technetium Tc99m Sestamibi: the head, shoulders and the sample block.

- 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 to separate breast tissue from the myocardium and liver, and to exclude potential activity that may be present in the opposite breast. For lateral images, position the patient prone with the isoluminal arm comfortably above the head, shoulders flat against the table, head turned to the side and relaxed, with the breast imaged pendent through an overlay cutout. The breast should not be compressed on the overlay. For anterior images, position the patient supine with both arms behind the head. For lateral or anterior images, shield the chest and abdominal organs, or remove them from the field of view.

- For complete study, sets of images should be obtained five minutes after the injection, and in the following sequence:

- Beginning five minutes after the injection of Technetium Tc99m Sestamibi:

- ten-minute lateral image of breast with abnormality

- ten-minute lateral image of contralateral breast

- ten-minute anterior image of both breasts

2.2 Radiation Dosimetry

The radiation doses to organs and tissues of an average patient (70 Kg) per 30 mCi of Technetium Tc99m Sestamibi injected intravenously are 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>radial mGy/</td>
<td>radial mGy/</td>
</tr>
<tr>
<td></td>
<td>30 mCi</td>
<td>1110 MBq</td>
</tr>
<tr>
<td></td>
<td>30 mCi</td>
<td>1110 MBq</td>
</tr>
<tr>
<td>Breast</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Upper Large Intestine</td>
<td>5.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>3.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Liver</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Ovaries</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Testes</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Total Body</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

For full prescribing information, see full prescribing information for CARDIOLITE®.
Radioisotopes should not be used.

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%) were 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.

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 reactions include: hypotension, bradycardia, diarrhea, urticaria, erythema, 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 anaphylaxis and generalized urticaria. In some patients, the allergic symptoms developed on the second injection during CARDIOLITE imaging. Patients who receive CARDIOLITE or MIBI® 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 MIBI®, 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 labeling 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.
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 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 constant with a t1/2 of 4.3 minutes at rest, and clears with a t1/2 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 myocardial biologic 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 (or clearance) which includes both the biological half-life and radiocative 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 radiocative decay) of Tc99m Sestamibi from the heart and liver.

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

12.4 Distribution

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 infarction model reported that the drug showed no redistribution of any consequence. "In comparison with most other diagnostic technetium labeled radionuclide agents, however, Sestamibi has significant advantages. These advantages include the ability to define early myocardial ischaemia, the ability to predict which patient will be likely to have further cardiac events and the ability to distinguish those patients with abnormal perfusion scans and long term cardiac events was an increase in cells with chromosome aberrations was observed in the in vitro human battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and SV3T3/J-L1 test systems. The active intermediate, Cu(MIBI) is well tolerated in vivo. Minimal exposure (ALARA) is necessary in those individuals who are occupationally exposed to chemotherapy.

In earlier trials, using a template consisting of the anterior wall, inferior-posterior wall and isolated localization in the anterior-inferior posterior wall in patients with suspected angina or coronary artery disease was shown. Disease localization isolated to the apex have not been established. In adults, Tc99m Sestamibi has not been studied or evaluated in cardiac disorders other than coronary artery disease.

BREAST IMAGING: MIRALUMA® was evaluated in a multicenter, clinical trials of a total of 673 women patients. Overall the mean age was 52 (range 23 to 87 years). The racial and ethnic representation was 70% Caucasian, 15% African-American, 14% Hispanic and 1% Asian.

Both clinical studies evaluated women who were referred for further evaluation for either: 1) a mammographically detected (with varying degrees of malignant likelihood) but not palpable breast lesion (study A, n=387, mean age = 54 years), or 2) a palpable breast lesion (study B, n=206, mean age = 56 years). In both studies all patients were scheduled for biopsy.

MIRALUMA® (20 – 30 mCi) was injected intravenously in a vein that was contrastral to the breast to be imaged. Prior to lyophilization the pH is between 5.3-5.9. The contents of the vial are to accumulate in viable myocardial tissue in a manner analogous to that of thallous chloride Tl-201. Although studies of subcellular fractionation and electron micrographic analysis of heart cell aggregates suggest that Technetium 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.

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-five 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 radionuclides, the radiation dose to the ovaries (1.5 rad/30 mCi at rest, 1.2 rad/30 mCi at exercise) is greater than the National Academy of Sciences ALARA standard. It is necessary to consider the reproductive health of women. (See Section 2.)

The active intermediate, Cu(MIBI)_3BF_4 was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and SV3T3/J-L1 test systems (Eugene, OR). An increase in cells with chromosome aberrations was observed in the in vivo human lymphocyte assay. Cu(MIBI)_3BF_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 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

<table>
<thead>
<tr>
<th>Table 6.0 Biological and Effective Clearance</th>
</tr>
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<tbody>
<tr>
<td><strong>Time</strong></td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>5 min.</td>
</tr>
<tr>
<td>30 min.</td>
</tr>
<tr>
<td>60 min.</td>
</tr>
<tr>
<td>120 min.</td>
</tr>
<tr>
<td>24 h</td>
</tr>
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