FDA-approved radiopharmaceuticals

This is a current list of all FDA-approved radiopharmaceuticals. USP <825> requires the use of conventionally manufactured drug products (e.g., NDA, ANDA) for Immediate Use. Nuclear medicine practitioners that receive radiopharmaceuticals that originate from sources other than the manufacturers listed in these tables may be using unapproved copies.

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Manufacturer</th>
<th>Trade names</th>
<th>Approved indications in adults (Pediatric use as noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon-11 choline</td>
<td>Various</td>
<td>–</td>
<td>Indicated for PET imaging of patients with suspected prostate cancer recurrence based upon elevated blood prostate specific antigen (PSA) levels following initial therapy and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging (MRI) to help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation</td>
</tr>
<tr>
<td>Carbon-14 urea</td>
<td>Halyard Health</td>
<td>PYtest</td>
<td>Detection of gastric urease as an aid in the diagnosis of H.pylori infection in the stomach</td>
</tr>
<tr>
<td>Fluorine-18 florbetaben</td>
<td>Life Molecular Imaging</td>
<td>Neuraceq™</td>
<td>Indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) or other causes of cognitive decline</td>
</tr>
<tr>
<td>Fluorine-18 flucicovine</td>
<td>Blue Earth Diagnostics</td>
<td>Axumin™</td>
<td>A radioactive diagnostic agent indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment</td>
</tr>
<tr>
<td>Fluorine-18 sodium fluoride</td>
<td>Various</td>
<td>–</td>
<td>PET bone imaging agent to delineate areas of altered osteogenesis</td>
</tr>
<tr>
<td>Radiopharmaceutical</td>
<td>Manufacturer</td>
<td>Trade names</td>
<td>Approved indications in adults (Pediatric use as noted)</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>---------------------------------------------------</td>
</tr>
</tbody>
</table>
| 7 Fluorine-18 fludeoxyglucose | Various | – | As a PET imaging agent to:  
• Assess abnormal glucose metabolism in oncology  
• Assess myocardial hibernation  
• Identify regions of abnormal glucose metabolism associated with foci of epileptic seizures |
| 8 Fluorine-18 flutemetamol | GE Healthcare | Vizamyl™ | Indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) or other causes of cognitive decline |
| 9 Gallium-67 citrate | Curium | – | Useful to demonstrate the presence/extent of:  
• Hodgkin’s disease  
• Lymphoma  
• Bronchogenic carcinoma  
Aid in detecting some acute inflammatory lesions |
| 10 Gallium-68 dotatate | Advanced Accelerator Applications | NETSPOT™ | A radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients |
| 11 Gallium-68 dotatoc | University of Iowa | – | A radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients |
| 12 Indium-111 chloride | Curium | – | Indicated for radiolabeling:  
• ProstaScint® used for in vivo diagnostic imaging procedures |
| 13 Indium-111 oxyquinoline | BWXT | – | Indicated for radiolabeling autologous leukocytes which may be used as an adjunct in the detection of inflammatory processes to which leukocytes migrate, such as those associated with abscesses or other infection |
| 14 Indium-111 pentetate | GE Healthcare | – | For use in radionuclide cisternography |
| 15 Indium-111 pentetreotide | Curium | Octreoscan™ | An agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors |
| 16 Iodine I-123 iobenguane | GE Healthcare | AdreView™ | Indicated for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests.  
Indicated for scintigraphic assessment of sympathetic innervation of the myocardium by measurement of the heart to mediastinum (H/M) ratio of radioactivity uptake in patients with New York Heart Association (NYHA) class II or class III heart failure and left ventricular ejection fraction (LVEF) ≤ 35%. Among these patients, it may be used to help identify patients with lower one and two year mortality risks, as indicated by an H/M ratio ≥ 1.6. Limitations of Use: In patients with congestive heart failure, its utility has not been established for: selecting a therapeutic intervention or for monitoring the response to therapy; using the H/M ratio to identify a patient with a high risk for death. |
<p>| 17 Iodine I-123 ioflupane | GE Healthcare | DaTscan™ | Indicated for striatal dopamine transporter visualization using SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS) in whom it may help differentiate essential tremor due to PS (idiopathic Parkinson’s disease, multiple system atrophy and progressive supranuclear palsy) |</p>
<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Manufacturer</th>
<th>Trade names</th>
<th>Approved indications in adults (Pediatric use as noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 Iodine I-123 sodium iodide capsules</td>
<td>Cardinal Health</td>
<td>–</td>
<td>Indicated for use in the evaluation of thyroid: • Function • Morphology</td>
</tr>
<tr>
<td></td>
<td>Curium</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>19 Iodine I-125 human serum albumin</td>
<td>IsoTex Diagnostics</td>
<td>Jeanatope</td>
<td>Indicated for use in the determination of: • Total blood • Plasma volume</td>
</tr>
<tr>
<td>20 Iodine I-125 iothalamate</td>
<td>IsoTex Diagnostics</td>
<td>Glofil-125</td>
<td>Indicated for evaluation of glomerular filtration</td>
</tr>
<tr>
<td>21 Iodine I-131 human serum albumin</td>
<td>IsoTex Diagnostics</td>
<td>Megatope</td>
<td>Indicated for use in determinations of: • Total blood and plasma volumes • Cardiac output • Cardiac and pulmonary blood volumes and circulation times • Protein turnover studies • Heart and great vessel delineation • Localization of the placenta • Localization of cerebral neoplasms</td>
</tr>
<tr>
<td>22 Iodine-131 iobenguane</td>
<td>Progenics® Pharmaceuticals</td>
<td>AZEDRA®</td>
<td>Indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy</td>
</tr>
<tr>
<td>23 Iodine I-131 sodium iodide</td>
<td>DRAXIMAGE</td>
<td>HICON™</td>
<td>Diagnostic: • Performance of the radioactive iodide (RAI) uptake test to evaluate thyroid function • Localizing metastases associated with thyroid malignancies Therapeutic: • Treatment of hyperthyroidism • Treatment of carcinoma of the thyroid</td>
</tr>
<tr>
<td>24 Lutetium Lu-177 dotatate</td>
<td>Advanced Accelerator Applications</td>
<td>LUTATHERA®</td>
<td>Indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.</td>
</tr>
<tr>
<td>25 Molybdenum Mo-99 generator</td>
<td>Curium</td>
<td>Ultra-Technekow™ V4</td>
<td>Generation of Tc-99m sodium pertechnetate for administration or radiopharmaceutical preparation Used to produce sodium pertechnetate Tc-99m injection, USP a radioactive diagnostic agent and can be used in the preparation of FDA-approved diagnostic radiopharmaceuticals. Indicated in: • Salivary Gland Imaging • Nasolacrimal Drainage System Imaging (dacryoscentigraphy) • Thyroid Imaging (adults &amp; pediatrics) • Vesicoureteral Imaging (direct isotopic cystography) (adults and pediatrics)</td>
</tr>
<tr>
<td></td>
<td>Lantheus Medical Imaging</td>
<td>TechneLite®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NorthStar Medical Radioisotopes LLC</td>
<td>RadioGenix™ System</td>
<td></td>
</tr>
<tr>
<td>26 Nitrogen-13 ammonia</td>
<td>Various</td>
<td>–</td>
<td>Indicated for diagnostic Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease</td>
</tr>
</tbody>
</table>

Package inserts may be viewed at nps.cardinal.com/MSDSPI/Main.aspx

Radiopharmaceuticals that may potentially have unapproved copies of FDA-approved commercially available radiopharmaceuticals in the marketplace.
<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Manufacturer</th>
<th>Trade names</th>
<th>Approved indications in adults (Pediatric use as noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium-223 dichloride</td>
<td>Bayer HealthCare Pharmaceuticals Inc.</td>
<td>Xofigo®</td>
<td>Indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease</td>
</tr>
<tr>
<td>Rubidium-82 chloride</td>
<td>Bracco Diagnostics</td>
<td>Cardiogen-82®</td>
<td>PET myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium in patients with suspected myocardial infarction</td>
</tr>
<tr>
<td>Samarium-153 lexidronam</td>
<td>Lantheus Medical Imaging</td>
<td>Quadramet®</td>
<td>Indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan</td>
</tr>
<tr>
<td>Technetium-99m bicine</td>
<td>Lantheus Medical Imaging</td>
<td>Neurolite®</td>
<td>SPECT imaging as an adjunct to conventional CT or MRI imaging in the localization of stroke in patients in whom stroke has already been diagnosed</td>
</tr>
</tbody>
</table>
| Technetium-99m exametazine | DRAXIMAGE* | Ceretec™ | • As an adjunct in the detection of altered regional cerebral perfusion in stroke  
• Leukocyte labeled scintigraphy as an adjunct in the localization of intra abdominal infection and inflammatory bowel disease* |
| Technetium-99m macroaggregated albumin | DRAXIMAGE | – | • An adjunct in the evaluation of pulmonary perfusion (adult and pediatric)  
• Evaluation of peritoneo-venous (LaVeen) shunt patency |
| Technetium-99m mertiatide | Curium | Technescan MAG3™ | In patients > 30 days of age as a renal imaging agent for use in the diagnosis of:  
• Congenital and acquired abnormalities  
• Renal failure  
• Urinary tract obstruction and calculi  
Diagnostic aid in providing:  
• Renal function  
• Split function  
• Renal angiograms  
• Renogram curves for whole kidney and renal cortex |
| Technetium-99m oxidronate | Curium | Technescan™ HDP | As a bone imaging agent to delineate areas of altered osteogenesis (adult and pediatric use) |
| Technetium-99m pentetate | DRAXIMAGE | – | • Brain imaging  
• Kidney imaging:  
  - To assess renal perfusion  
  - To estimate glomerular filtration rate  
• Lung ventilation imaging and evaluation of pulmonary embolism when paired with perfusion imaging in adult and pediatric patients |
| Technetium-99m pyrophosphate | Curium | Technescan™ PYP™ | • As a bone imaging agent to delineate areas of altered osteogenesis  
• As a cardiac imaging agent used as an adjunct in the diagnosis of acute myocardial infarction  
• As a blood pool imaging agent useful for:  
  - Gated blood pool imaging  
  - Detection of sites of gastrointestinal bleeding |
<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Manufacturer</th>
<th>Trade names</th>
<th>Approved indications in adults (Pediatric use as noted)</th>
</tr>
</thead>
</table>
| 39 Technetium-99m red blood cells | Curium | UltraTag™ | Tc99m-labeled red blood cells are used for:  
- Blood pool imaging including cardiac first pass and gated equilibrium imaging  
- Detection of sites of gastrointestinal bleeding |
| 40 Technetium-99m sestamibi | Cardinal Health | – | Myocardial perfusion agent that is indicated for:  
- Detecting coronary artery disease by localizing myocardial ischemia  
(reversible defects) and infarction (non-reversible defects)  
- Evaluating myocardial function  
- Developing information for use in patient management decisions  
- Planar breast imaging as a second line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass |
| 41 Technetium-99m sodium pertechnetate | Curium | – | Brain Imaging (including cerebral radionuclide angiography)*  
- Thyroid Imaging*  
- Salivary Gland Imaging  
- Placenta Localization  
- Blood Pool Imaging (including radionuclide angiography)*  
- Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux*  
- Nasolacrimal Drainage System Imaging  
(*adult and pediatric use) |
| 42 Technetium-99m succimer | GE Healthcare | – | An aid in the scintigraphic evaluation of renal parenchymal disorders |
| 43 Technetium-99m sulfur colloid | Pharmalucence | – | Imaging areas of functioning reticuloendothelial cells in the liver, spleen and bone marrow*  
- It is used orally for:  
  - Esophageal transit studies*  
  - Gastroesophageal reflux scintigraphy*  
  - Detection of pulmonary aspiration of gastric contents*  
- Aid in the evaluation of peritoneo-venous (LeVeen) shunt patency  
- To assist in the localization of lymph nodes draining a primary tumor in patients with breast cancer or malignant melanoma when used with a hand-held gamma counter  
(*adult and pediatric use) |
| 44 Technetium-99m tetrofosmin | GE Healthcare | Myoview™ | Myocardial perfusion agent that is indicated for:  
- Detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects)  
- The assessment of left ventricular function (left ventricular ejection fraction and wall motion) |
| 45 Technetium-99m tilmanocept | Cardinal Health | Lymphoseek® | Indicated with or without scintigraphic imaging for:  
- Lymphatic mapping using a handheld gamma counter to locate lymph nodes draining a primary tumor site in patients with solid tumors for which this procedure is a component of intraoperative management.  
- Guiding sentinel lymph node biopsy using a handheld gamma counter in patients with clinically node negative squamous cell carcinoma of the oral cavity, breast cancer or melanoma. |
<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Manufacturer</th>
<th>Trade names</th>
<th>Approved indications in adults (Pediatric use as noted)</th>
</tr>
</thead>
</table>
| Thallium-201 chloride | Curium | – | • Useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction  
• As an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease)  
• Localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels |
| GE Healthcare | – |  |
| Lantheus Medical Imaging | – |  |
| Xenon-133 gas | Curium | – | • The evaluation of pulmonary function and for imaging the lungs  
• Assessment of cerebral flow |
| Lantheus Medical Imaging | – |  |
| Yttrium-90 chloride | Eckert & Ziegler Nuclitec | – | Indicated for radiolabeling:  
• Zevalin® used for radioimmunotherapy procedures |
| Yttrium-90 ibritumomab tiuxetan | Acrotech Biopharma | Zevalin® | Indicated for the:  
• Treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL)  
• Treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy |

Package inserts may be viewed at nps.cardinal.com/MSDSPI/Main.aspx

Any reader of this document is cautioned that Cardinal Health makes no representation, guarantee, or warranty, express or implied as to the accuracy and appropriateness of the information contained in this document, and will bear no responsibility or liability for the results or consequences of its use. The information provided on this document is non-promotional. It is intended for informational purposes only and is not intended to promote or recommend any individual product. Contact the applicable manufacturer if you have any questions regarding a product listed on this document.
**Sodium Iodide I 123**

Diagnostic-Capsules for Oral Administration

**DESCRIPTION**
Sodium Iodide I 123 (Na-123 I) for diagnostic use is supplied in capsules for oral administration. The capsules are available in strengths of 3.7, 7.4 and 14.8 megabecquerels (MBq) (100, 200 and 400 uCi) I 123 at time of calibration. Each capsule contains 0.3ug - 3ug Sodium Thiosulfate as a stabilizer.

The radionuclidic composition at calibration is not less than 97.0 percent I 123, not more than 2.9 percent I 128 and not more than 0.1 percent all others (I 121 or I 122). The radionuclidic composition at expiration time is not less than 87.2 percent I 123, not more than 12.4 percent I 125 and not more than 0.4 percent all others. The ratio of the concentration of I 123 and I 125 changes with time. Graph 1 shows the maximum concentration of each as a function of time.

**EXTERNAL RADIATION**
The specific gamma ray constant for I 123 is 1.69/r/hr-mCi at 1 cm. The first half value thickness of lead (Pb) for I 123 is 0.005 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of Pb is shown in Table 2. For example, the use of 1.63 cm. of lead will decrease the external radiation exposure by a factor of about 1,000.

<table>
<thead>
<tr>
<th>Shield Thickness (Pb), cm.</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.036</td>
<td>0.5</td>
</tr>
<tr>
<td>0.120</td>
<td>0.1</td>
</tr>
<tr>
<td>0.240</td>
<td>0.1</td>
</tr>
<tr>
<td>0.358</td>
<td>0.1</td>
</tr>
<tr>
<td>0.477</td>
<td>0.1</td>
</tr>
</tbody>
</table>


**Table 2**

**Note** that these estimates of attenuation do not take into consideration the presence of contaminants.

To correct for physical decay of I 123, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

**Table 3**

<table>
<thead>
<tr>
<th>Sodium Iodide I 123 Decay Chart: Half-Life 13.2 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>0*</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>15</td>
</tr>
</tbody>
</table>

*Time of Calibration

**CLINICAL PHARMACOLOGY**
Sodium iodide I 123 is readily absorbed from the upper gastrointestinal tract. Following absorption, the iodide is distributed primarily within the extracellular fluid of the body. It is trapped and organically bound by the thyroid and concentrated by the stomach, chorial plexus and salivary glands. It is excreted by the kidneys.

The fraction of the administered dose which is accumulated in the thyroid gland may be a measure of thyroid function in the absence of unusually high or low iodine intake or administration of certain drugs which influence iodine accumulation by the thyroid gland. Accordingly, the patient should be questioned carefully regarding previous medication and/or procedures involving radiographic media. Normal subjects can accumulate approximately 10-30% of the administered iodine dose in the thyroid gland, however, the normal and abnormal ranges are established by individual physician's criteria. The mapping (imaging) of Sodium Iodide I 123 distribution in the thyroid gland may provide useful information concerning thyroid anatomy and definition of normal and/or abnormal functioning of tissue within the gland.

**INDICATION AND USE**
Administration of Sodium Iodide I 123 is indicated as a diagnostic procedure to be used in evaluating thyroid function and/or morphology.

**CONTRAINDICATIONS**
To date there are no known contraindications to the use of Sodium Iodide I 123 capsules.

**WARNINGS**
Females of childbearing age and children under 18 should not be studied unless the benefits anticipated from the performance of the test outweigh the possible risk of exposure to the amount of ionizing radiation associated with the test.

**Graph 1**
Radionuclidic Concentration of I 123 and I 125

**PHYSICAL CHARACTERISTICS**
Sodium Iodide I 123 decays by electron capture with a physical half-life of 13.2 hours. The photon that is useful for detection and imaging studies is listed in Table 1.

**Table 1**
Principal Radiation Emission Data

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Mean % Disintegration</th>
<th>Mean Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma-2</td>
<td>83.4</td>
<td>159</td>
</tr>
</tbody>
</table>

*Kocher, David C., Radioactive Decay Data Tables, DOE/TIC-11026, 122, (1981)*
PRECAUTIONS

General
The contents of the capsule are radioactive. Adequate shielding of the preparation must be maintained at all times.

Do not use after the expiration time and date (30 hours after calibration time) stated on the label.

The prescribed Sodium Iodide I 123 dose should be administered as soon as practical from the time of receipt of product (i.e., as close to calibration time as possible) in order to minimize the fraction of radiation exposure due to relative increase of radionuclide contaminants with time.

Sodium Iodide I 123, as well as other radioactive drugs, must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to the patient consistent with proper patient management.

Radioactive pharmaceuticals 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenic potential, or whether Sodium Iodide I 123 affects fertility in males or females.

Pregnancy Category C
Animal reproduction studies have not been conducted with this drug. It is also not known whether Sodium Iodide I 123 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Sodium Iodide I 123 should be given to a pregnant woman only if clearly needed.

Ideally examinations using radioisotopes, especially those effective in nature, in women of childbearing capability should be performed during the first few (approximately ten) days following the onset of menses.

Nursing Mothers
Since I 123 is excreted in human milk, formula-feeding should be substituted for breast-feeding if the agent must be administered to the mother during lactation.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Although rare, reactions associated with the administration of Sodium Iodide I 123 for diagnostic use include, in decreasing order of frequency, nausea, vomiting, chest pain, tachycardia, itching skin, rash and hives.

Dosage and Administration
The recommended oral dose for the average patient (70 kg) is 3.7 to 14.8 MBq (100-400 μCi). The lower part of the dosage range 3.7 MBq (100 μCi) is recommended for uptake studies alone, and the higher part 14.8 MBq (400 μCi) for thyroid imaging. The determination of I 123 concentration in the thyroid gland may be initiated at six hours after administering the dose and should be measured in accordance with standardized procedures.

The patient dose should be measured by a suitable radioactive calibration system immediately prior to administration. The capsules can be utilized up to thirty (30) hours after calibration time and date. Thereafter discard the capsules in accordance with standard safety procedures. The user should wear waterproof gloves at all times when handling the capsules or container.

RADIATION DOSIMETRY
The estimated absorbed radiation doses to several organs of an average patient (70 kg) from oral administration of the maximum dose of 14.8 MBq (400 μCi) of I 123 are shown in Table 4 for thyroid uptakes of 5, 15, and 25%. For comparison at these three values of thyroid uptake, the estimated radiation doses from doses of 3.7 MBq (100 μCi) I 131, also used as thyroid imaging agent, are also included.

Table 4
Radiation Dose Estimates as a Function of Maximum Thyroid Uptake
for I 123 Sodium Iodide

<table>
<thead>
<tr>
<th>Target Organ Uptake (%)</th>
<th>I 123 nGy/14.8 MBq (100-400 μCi)</th>
<th>I 131 nGy/3.7 MBq (10-30 μCi)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum</td>
<td>TOC</td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>15</td>
<td>77</td>
<td>230</td>
</tr>
<tr>
<td>26</td>
<td>138</td>
<td>41</td>
</tr>
<tr>
<td>37</td>
<td>208</td>
<td>13</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.098</td>
<td>0.13</td>
</tr>
<tr>
<td>15</td>
<td>0.10</td>
<td>0.18</td>
</tr>
<tr>
<td>25</td>
<td>0.11</td>
<td>0.24</td>
</tr>
<tr>
<td>35</td>
<td>0.12</td>
<td>0.30</td>
</tr>
<tr>
<td>45</td>
<td>0.13</td>
<td>0.36</td>
</tr>
<tr>
<td>55</td>
<td>0.14</td>
<td>0.41</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.18</td>
<td>0.19</td>
</tr>
<tr>
<td>15</td>
<td>0.17</td>
<td>0.18</td>
</tr>
<tr>
<td>25</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>35</td>
<td>0.15</td>
<td>0.18</td>
</tr>
<tr>
<td>45</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>55</td>
<td>0.13</td>
<td>0.18</td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>15</td>
<td>0.09</td>
<td>0.11</td>
</tr>
<tr>
<td>25</td>
<td>0.13</td>
<td>0.15</td>
</tr>
<tr>
<td>35</td>
<td>0.15</td>
<td>0.17</td>
</tr>
<tr>
<td>45</td>
<td>0.16</td>
<td>0.19</td>
</tr>
<tr>
<td>55</td>
<td>0.17</td>
<td>0.21</td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.26</td>
<td>0.27</td>
</tr>
<tr>
<td>15</td>
<td>0.32</td>
<td>0.35</td>
</tr>
<tr>
<td>25</td>
<td>0.36</td>
<td>0.39</td>
</tr>
<tr>
<td>35</td>
<td>0.40</td>
<td>0.42</td>
</tr>
<tr>
<td>45</td>
<td>0.44</td>
<td>0.45</td>
</tr>
<tr>
<td>55</td>
<td>0.48</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Concentration at Time of Calibration: 0.7% I 123, 2.9% I 125, 0.1% I 131
Concentration at Time of Expiry: 0.7% I 123, 1.2% I 125, 0.4% I 131
All iodine kinetics treated as in WERD Dose Estimate Report 5. Bladder voiding interval, 4.8 hours.

Table 4 I 123 dosimetry taken from (CRF-30).

HOW SUPPLIED
Sodium Iodide I 123 is supplied as capsules for oral administration in strengths of 3.7 MBq (100 μCi), 7.4 MBq (200 μCi) and 14.8 MBq (400 μCi) at time of calibration. Each gelatin capsule contains 0.45 - 0.65 g of sucrose. The capsules are packaged in plastic vials containing one or five capsules of a single strength per vial. The plastic vial is packaged in a lead shield with a label identical to that affixed to the plastic vial. A package insert is supplied with each lead shield.

The I (iodine) content for a 100 μCi capsule is 5.2 ng the I content for a 200 μCi capsule is 10.4 ng the I content for a 400 μCi capsule is 20.8 ng at TOC.

Dispense and preserve capsules in well-closed containers that are adequately shielded. Store at room temperature, below 69°F.

The contents of the capsules are radioactive. Adequate shielding and handling precautions must be maintained.

This package insert issued November 2007

Cardinal Health

Denver, CO 80011 (303) 343-6800

Sodium Iodide I 123
1-020-15 Printed in U.S.A.
Fludeoxyglucose F-18 Injection (18F-FDG) is indicated for positron emission tomography (PET) imaging in the following settings:

- **Oncology**: For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- **Cardiology**: For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- **Neurology**: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

**Dosage and Administration**

Fludeoxyglucose F-18 Injection is a radiopharmaceutical that emits radiation. Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities.

- In the oncology and neurology settings, instruct patients to fast for 4–6 hours prior to the drug’s injection. Consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to the drug’s administration.
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50–75 grams) prior to the drug’s injection facilitates localization of cardiac ischemia.
- Aseptically withdraw Fludeoxyglucose F-18 Injection from its container and administer by intravenous injection. The recommended dose:
  - for adults is 5–10 mCi (185–370 MBq), in all indicated clinical settings.
  - for pediatric patients is 2.6 mCi in the neurology setting.

**Contraindications**

- Radiation risks: use smallest dose necessary for imaging.
- Blood glucose abnormalities: may cause suboptimal imaging.

**Warnings and Precautions**

- Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available.

**Dosage Forms and Strengths**

Multiple-dose glass vial containing 0.74 - 18.5 Gbq (20 - 500 mCi/mL) of Fludeoxyglucose F-18 Injection and 4.5 mg of sodium chloride in citrate buffer (approximately 2.3 ml volume) for intravenous administration.

**Adverse Reactions**

None

**Use in Specific Populations**

- Pregnancy Category C: No human or animal data. Consider alternative diagnostics; use only if clearly needed.
- Nursing mothers: Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F-18 Injection is administered to a woman who is breast-feeding.
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology settings.

To report SUSPECTED ADVERSE REACTIONS, contact Cardinal Health at 1-800-618-2768 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**Revised: 02/2019**
2.5 Radiation Safety – Drug Handling

- Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Fludeoxyglucose F-18 Injection to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel and other persons.
- The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used.
- LLI = lower large intestine; ** ULI = upper large intestine

3.0 DOSAGE FORMS AND STRENGTHS

- Multiple-dose glass vial containing 0.74 - 18.5 GBq (20 - 500 mCi/mL) of Fludeoxyglucose F-18 Injection and 4.5 mg of sodium chloride in citrate buffer (approximately 2 - 30 mL volume) for intravenous administration.

4.0 CONTRAINDICATIONS

- Fludeoxyglucose F-18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless citrate buffered solution. Each mL contains between 0.74 - 18.5 GBq (20 - 500 mCi/mL) of 2-deoxy-2-[18F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride in citrate buffer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

5.0 Physical Characteristics

Fluorine F-18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[18F]fluoro-D-glucose has the molecular formula of C₇H₁₀O₅F, with a molecular weight of 181.26, and has the following chemical structure:

- Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-1 1026, 89 (1981)

The specific gamma ray constant (point source air kerma coefficient) for fluorine F-18 is 5.7 x 10-2 mGy/MBq/cm (1.3 x 10-4 Gy/kBq/cm) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4 mm lead (Pb) or 2.9 mm tungsten (W) alloy. The range of attenuation coefficients for this radionuclide as a function of shield thickness is shown in Table 3. For example, the interposition of an 8 mm thickness of Pb or 5.8 mm thickness of W alloy, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 4.
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Fludeoxyglucose F-18 is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathological conditions. Fludeoxyglucose F-18 is taken up by the cell membrane by glucose transporter proteins and is phosphorylated within the cell to \([\text{^18F}]\text{FDG}-6\)-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathological process, the retention and clearance of Fludeoxyglucose F-18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and Fludeoxyglucose F-18 transport and phosphorylation (expressed as the "lumped constant" ratio), Fludeoxyglucose F-18 is used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased retention and clearance of Fludeoxyglucose F-18 reflect a balance involving glucose transporter, triexponentially. The effective half-life ranges of the three phases were 0.2-0.3 minutes, impaired, hepatically impaired or pediatric patients. Fludeoxyglucose F-18 is eliminated through Special Populations:

- dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two
- Elimination:

Fludeoxyglucose F-18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-6-phosphate presumably is metabolized to 2-deoxy-2-[F-18]fluoro-6-phospho-D-mannose([F-18]FDM-6-phosphate).

Fludeoxyglucose F-18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-6-phosphate presumably is metabolized to 2-deoxy-2-[F-18]fluoro-6-phospho-D-mannose([F-18]FDM-6-phosphate).

Fludeoxyglucose F-18 Injection is supplied in a multi-dose, capped 30 mL glass vial containing

The efficacy of Fludeoxyglucose F-18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular dysfunction who were undergoing coronary revascularization.

Before revascularization, patients underwent PET imaging with Fludeoxyglucose F-18 Injection (74 – 370 MBq, 2 – 10 mCi) and perfusion imaging with other direct angiographic techniques.

Doses of Fludeoxyglucose F-18 Injection ranged from 74-370 MBq (2-10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery.

Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fludeoxyglucose F-18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F-18 accumulation and perfusion (i.e., matched defects).

Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted by Fludeoxyglucose F-18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F-18 Injection is more limited.

14.3 Neurology
A prospective, open label trial, Fludeoxyglucose F-18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F-18 Injection in the range of 185-370 MBq (5-10 mCi). The mean age was 16.4 years (range: 4 months - 58 years; of these, 42 patients were less than 12 years and 16 patients were less than 2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation for surgical treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and spatio-temporal EEs. Fludeoxyglucose F-18 Injection PET imaging confirmed previous diagnostic findings in 16% (348/2158) of the patients; in 34% (380/2158) of the patients, Fludeoxyglucose F-18 Injection PET imaging provided new findings. In 32% (72/220), imaging with Fludeoxyglucose F-18 was inconclusive. The impact of these imaging findings on clinical outcomes is not known.

Several other studies comparing imaging with Fludeoxyglucose F-18 Injection results to subphenoedal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F-18 Injection to distinguish idiopathic epilepticogenic foci from other brain lesions that may cause seizures have not been established.

15 REFERENCES
- ICRP Publication 53, Volume 16, No. 1, 1974, pages 75-76.

16 HOW SUPPLIED/STORAGE AND HANDLING
Fludeoxyglucose F-18 Injection is supplied in a multi-dose, capped 30 mL glass vial containing

between 74-185.5 GBq (2-500 mCi/mL), of no carrier added 2-deoxy-2-[F-18] fluoro-D-glucose, at end of synthesis, in approximately 2.3 mL. The contents of each vial are sterile, pyrogen-free and preservative-free.

NDC 685-150-30-10
0.74 - 18.5 GBq (20 - 500 mCi/mL)

Recept, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements for the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

Store the Fludeoxyglucose F-18 Injection vial upright in a lead or tungsten alloy shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

The expiration date and time are provided on the container label. Use Fludeoxyglucose F-18 Injection within 12 hours from the EOS time.

17 PATIENT COUNSELING INSTRUCTION
Instruct patients in procedures that increase renal clearance of radioactivity. Encourage patients to:
- drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.
- More information and Distributed by:
  - Cardinal Health 414, LLC
  - 7000 Cardinal Place
  - Dublin, OH 43017

NPS-PI-0003 ver 4.0
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Ammonia N-13 Injection, USP safely and effectively. See full prescribing information for Ammonia N-13 Injection, USP.

Ammonia N-13 Injection, USP for intravenous use
Initial U.S. Approval: 2007

INDICATIONS AND USAGE
Ammonia N-13 Injection, USP is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.

Dosage and Administration

Rest Imaging Study (2.1):
- Asynchronously withdraw Ammonia N-13 Injection, USP from its container and administer 10-20 mCi (0.368 - 0.736 GBq) as a bolus through a catheter inserted into a large peripheral vein.
- Start imaging 3 minutes after the injection and acquire images for a total of 10-20 minutes.

Stress Imaging Study (2.2):
- If a rest imaging study is performed, begin the stress imaging study 40 minutes or more after the first Ammonia N-13 Injection, USP to allow sufficient isotope decay.
- Administer a pharmacologic stress-inducing drug in accordance with its labeling.
- Asynchronously withdraw Ammonia N-13 Injection, USP from its container and administer 10-20 mCi (0.368 - 0.736 GBq) of Ammonia N-13 Injection, USP as a bolus at 8 minutes after the administration of the pharmacologic stress-inducing drug.
- Start imaging 3 minutes after the Ammonia N-13 Injection, USP and acquire images for a total of 10-20 minutes.

Patient Preparation (2.3):
- To increase renal clearance of radioactivity and to minimize radiation dose to the bladder, hydrate the patient before the procedure and encourage voiding as soon as each image acquisition is completed and as often as possible thereafter for at least one hour.

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Rest Imaging Study
2.2 Stress Imaging Study
2.3 Patient Preparation
2.4 Radiation Dosimetry
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Radiation Risks
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Nursing Mothers
8.3 Pediatric Use
8.4 Geriatric Use
8.5 Renal Impairment
8.6 Hepatic Impairment
8.7 Hyperthyroidism
8.8 Other Issues
10 ADVERSE REACTIONS
11 DESCRIPTION
11.1 Chemical Characteristics
11.2 Physical Characteristics
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
18 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed

Table 1: N-13 Absorbed Radiation Dose Per Unit Activity (rem/mCi) for Adults and Pediatric Groups

<table>
<thead>
<tr>
<th>Organ</th>
<th>Adult</th>
<th>15-year old</th>
<th>16-year old</th>
<th>5-year old</th>
<th>1-year old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.0055</td>
<td>0.0069</td>
<td>0.016</td>
<td>0.025</td>
<td>0.048</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>0.008</td>
<td>0.0077</td>
<td>0.0068</td>
<td>0.009</td>
<td>0.11</td>
</tr>
<tr>
<td>Bone surface</td>
<td>0.0095</td>
<td>0.011</td>
<td>0.011</td>
<td>0.012</td>
<td>0.027</td>
</tr>
<tr>
<td>Brain</td>
<td>0.011</td>
<td>0.011</td>
<td>0.011</td>
<td>0.011</td>
<td>0.025</td>
</tr>
<tr>
<td>Breast</td>
<td>0.0067</td>
<td>0.0067</td>
<td>0.010</td>
<td>0.017</td>
<td>0.033</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.0068</td>
<td>0.0074</td>
<td>0.0083</td>
<td>0.013</td>
<td>0.024</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.0067</td>
<td>0.0081</td>
<td>0.0013</td>
<td>0.021</td>
<td>0.041</td>
</tr>
</tbody>
</table>

DOSAGE FORMS AND STRENGTHS
Glass vial containing 0.138-1.387 GBq (3.75-37.5 mCi/mL) of Ammonia N-13 Injection, USP in aqueous 0.9 % sodium chloride solution (approximately 8 mL to 10 mL volume) (3).

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Ammonia N-13 Injection, USP may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient, health care worker (5).

ADVERSE REACTIONS
No adverse reactions have been reported for Ammonia N-13 Injection, USP based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting system (6).

To report SUSPECTED ADVERSE REACTIONS, contact Cardinal Health at 1-800-468-2768 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

17.1 Pregnancy

17.2 Post-study Voiding

17.3 Post-study Breastfeeding Avoidance

Revised: 12/2015

2.5 Drug Handling

- Inspect Ammonia N-13 Injection, USP visually for particulate matter and discoloration before administration, wherever solution and container permit.
- Do not administer Ammonia N-13 Injection, USP containing particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Wear waterproof gloves and effective shielding when handling Ammonia N-13 Injection, USP.
- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Ammonia N-13 Injection, USP. The contents of each vial are sterile and non-pyrogenic.
- Use appropriate safety measures, including shielding, consistent with proper patient management to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel, and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Before administration of Ammonia N-13 Injection, USP, assay the dose in a properly calibrated dose calibrator.

3 DOSAGE FORMS AND STRENGTHS
Glass vial (1 mL) containing 0.138-1.387 GBq (3.75-37.5 mCi/mL) of Ammonia N-13 Injection, USP in aqueous 0.9 % sodium chloride solution (approximately 8 mL to 10 mL volume) that is suitable for intravenous administration.

4 CONTRAINDICATIONS
None
5 Warnings and Precautions

5.1 Radiation Risks

Ammonia N-13 Injection, USP may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration (2.4)].

6 Adverse Reactions

No adverse reactions have been reported for Ammonia N-13 Injection, USP based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known.

7 Drug Interactions

The possibility of interactions of Ammonia N-13 Injection, USP with other drugs taken by patients undergoing PET imaging has not been studied.

8 Use in Specific Populations

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Ammonia N-13 Injection, USP. It is also not known whether Ammonia N-13 Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Ammonia N-13 Injection, USP should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for radiation exposure to nursing infants from Ammonia N-13 Injection, USP, use alternative infant nutrition sources (e.g., stored breast milk or infant formula) for 2 hours (10 half-lives of radioactive decay for N-13 isotope) after administration of the drug or avoid use of the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Ammonia N-13 Injection, USP has been established in pediatric patients based on known metabolism of ammonia, radiation dosimetry in the pediatric population, and clinical studies in adults [see Dosage and Administration (2.4)].

11 Description

11.1 Chemical Characteristics

Ammonia N-13 Injection, USP is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient, $^{[13N]}$ ammonia, has the molecular formula of $^{14}N_2H_3$, with a molecular weight of 16.02, and has the following chemical structure:

Ammonia N-13 Injection, USP is provided as a ready to use sterile, pyrogen-free, clear and colorless solution. Each mL of the solution contains 0.338 GBq (1.387 GBq/L) of $^{13N}$ ammonia at the end of synthesis (EOS) reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 to 7.5. The recommended dose of radioactivity (10-20 mCi) is associated with a theoretical mass dose of 0.5-1.0 picomoles of ammonia.

11.2 Physical Characteristics

Nitrogen N-13 decays by emitting positron to Carbon C-13 (stable) and has a physical half-life of 9.96 minutes. The principal photons useful for imaging are the dual 511 keV gamma photons that are produced and emitted simultaneously in opposite direction when the positron interacts with an electron (Table 2).

12.1 Pharmacodynamics

Following intravenous injection, ammonia N-13 enters the myocardium through the coronary arteries. The PET technique measures myocardial blood flow based on the assumption of a three-compartmental disposition of intravenously administered ammonia N-13 in the myocardium. In this model, the value of the rate constant, which represents the delivery of blood to myocardium, and the fraction of ammonia N-13 extracted into the myocardial cells, is a measure of myocardial blood flow. Optimal PET imaging of the myocardium is generally achieved between 10 to 20 minutes after administration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies have not been performed to evaluate the carcinogenic potential of Ammonia N-13 Injection, USP. Genotoxicity assays and impairment of male and female fertility studies with Ammonia N-13 Injection, USP have not been performed.

14 Clinical Studies

In a descriptive, prospective, blinded image interpretation study of adult patients with known or suspected coronary artery disease, myocardial perfusion defects in stress and rest PET images obtained with Ammonia N-13 (N=111) or Rubidium 82 (N=82) were compared to changes in stressors score (SFR) as determined by coronary angiography. The principal outcome of the study was the evaluation of PET defect severity relative to SFR.

PET perfusion defects at rest and stress for seven cardiac regions (anterior, apical, anteroseptal, posterior, anteroseptal, posterior, and inferior walls) were graded on a 0 to 5 scale defined as normal (0), possible (1), probable (2), mild (3), moderate (4), and severe (5) defects. Coronary angiograms were used to measure absolute and relative stenosis dimensions and to calculate stenosis score defined as the maximum value of flow at maximum coronary vasodilatation relative to rest flow under standardized hemodynamic conditions. SFR scores ranged from 0 (total occlusion) to 5 (normal).

With increasing impairment of flow reserve, the subjective PET defect severity increased. A PET defect score of 2 or higher was positively correlated with flow reserve impairment (SFR<3).

15 References


16 How Supplied/Storage and Handling

Ammonia N-13 Injection, USP is packaged in 10 mL multiple dose glass vial containing between 1.11-1.11 GBq (30-300 mCi) of $^{13N}$ ammonia, at the end of synthesis (EOS) reference time, in 0.9% sodium chloride injection solution in approximately 8 mL to 10 mL volume. The recommended dose of radioactivity (10-20 mCi) is associated with a theoretical mass dose of 0.5-1.0 picomoles of Ammonia N-13.

NDC 68557-200-10

Storage

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Use the solution within 60 minutes of the End of Synthesis (EOS) calibration.

17 Patient Counseling Information

17.1 Pre-study Hydration

Instruct patients to drink plenty of water or other fluids (as tolerated) in the 4 hours before their PET study.

17.2 Post-study Voidsing

Instruct patients to void after completion of each image acquisition session and as often as possible for one hour after the PET scan ends.

17.3 Post-study Breastfeeding Avoidance

Instruct nursing patients to substitute stored breast milk or infant formula for breast milk for 2 hours after administration of Ammonia N-13 Injection, USP.

Manufactured by:

Cardinal Health 414, LLC
7000 Cardinal Place
Dublin, OH 43017

Distributed by:

Cardinal Health 414, LLC
7000 Cardinal Place
Dublin, OH 43017

Revised: 06/2013

NPS-PS-0001 ver 2.0
KIT FOR THE PREPARATION OF TECHNETIUM TC99M SESTAMIBI- kit for the preparation of technetium tc99m sestamibi injection, powder, lyophilized, for solution
Cardinal Health 414, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Kit for the Preparation of Technetium Tc 99m Sestamibi Injection safely and effectively. See full prescribing information for Kit for the Preparation of Technetium Tc 99m Sestamibi Injection.

Indications and Usage:
Technetium Tc 99m Sestamibi is a myocardial perfusion agent indicated for:

- detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects) (1)
- evaluating myocardial function and developing information for use in patient management decisions (1)

Dosage and Administration:

- For Myocardial Imaging: The suggested dose range for I.V. administration of Technetium Tc 99m Sestamibi in a single dose to be employed in the average patient (70 Kg) is 370–1110 MBq (10–30 mCi). (2)
- For Breast imaging: The recommended dose range for I.V. administration of Technetium Tc 99m Sestamibi is a single dose of 740–1110 MBq (20–30 mCi). (2)

Dosage Forms and Strengths:

- Kit for Preparation of Technetium Tc 99m Sestamibi Injection is supplied as a lyophilized mixture in a 5 mL vial. (3)

Contraindications:

- None known. (4)

Warnings and Precautions:

- Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction and cerebrovascular events (5.1).
- Technetium Tc 99m 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 Technetium Tc 99m Sestamibi imaging (5.1).
- Caution should be exercised and emergency equipment should be available when administering Technetium Tc 99m Sestamibi (5.1).
- Before administering Technetium Tc 99m Sestamibi Injection, patients should be asked about the possibility of allergic reactions to either drug (5.1).
- The contents of the vial are intended only for use in the preparation of Technetium Tc 99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure (5.2).

Adverse Reactions:

The following adverse reactions have been reported in ≤ 0.5% of patients: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis; angioedema, arrhythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthenia, and vomiting within two hours after a second injection of Technetium Tc 99m Sestamibi. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, pruritus, rash, urticaria and fatigue have also been attributed to administration of the agent (6).

To report SUSPECTED ADVERSE REACTIONS, contact Cardinal Health at 1-800-618-2768 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions:

- To detect coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects) (1)
Specific drug-drug interactions have not been studied (7).

* In one study of 46 subjects who received Technetium Tc 99m Sestamibi administration, the radioactivity in both children and adolescents exhibited blood PK profiles similar to those previously reported in adults (8.4).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2018
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Myocardial Imaging: Technetium Tc 99m Sestamibi 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. Technetium Tc 99m Sestamibi 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: Technetium Tc 99m Sestamibi is indicated for planar imaging as a second line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass.

Technetium Tc 99m Sestamibi 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 I.V. administration of Technetium Tc 99m Sestamibi 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 I.V. administration of Technetium Tc 99m Sestamibi 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 isolateral 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 either 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 Tc 99m 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 1110 MBq (30 mCi) of Technetium Tc 99m Sestamibi injected intravenously are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1 Radiation Absorbed Doses from Tc 99m Sestamibi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Radiation Absorbed Dose</td>
</tr>
<tr>
<td>REST</td>
</tr>
<tr>
<td>Organ</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Breasts</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
</tr>
<tr>
<td>Small Intestine</td>
</tr>
<tr>
<td>Upper Large Intestine Wall</td>
</tr>
<tr>
<td>Lower Large Intestine Wall</td>
</tr>
<tr>
<td>Stomach Wall</td>
</tr>
<tr>
<td>Heart Wall</td>
</tr>
<tr>
<td>Kidneys</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Lungs</td>
</tr>
<tr>
<td>Bone Surfaces</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Ovaries</td>
</tr>
<tr>
<td>Testes</td>
</tr>
<tr>
<td>Red Marrow</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
</tr>
<tr>
<td>Total Body</td>
</tr>
</tbody>
</table>

**STRESS**

<table>
<thead>
<tr>
<th>Organ</th>
<th>2.0 hour void</th>
<th></th>
<th>4.8 hour void</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rads/30 mCi</td>
<td>mGy/1110 MBq</td>
<td>rads/30 mCi</td>
<td>mGy/1110 MBq</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.2</td>
<td>2.0</td>
<td>0.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.8</td>
<td>28.9</td>
<td>2.8</td>
<td>27.8</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>2.4</td>
<td>24.4</td>
<td>2.4</td>
<td>24.4</td>
</tr>
<tr>
<td>Upper Large Intestine Wall</td>
<td>4.5</td>
<td>44.4</td>
<td>4.5</td>
<td>44.4</td>
</tr>
<tr>
<td>Lower Large Intestine Wall</td>
<td>3.3</td>
<td>32.2</td>
<td>3.3</td>
<td>32.2</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>0.6</td>
<td>5.3</td>
<td>0.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.5</td>
<td>5.6</td>
<td>0.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Kidneys</td>
<td>1.7</td>
<td>16.7</td>
<td>1.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Liver</td>
<td>0.4</td>
<td>4.2</td>
<td>0.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.3</td>
<td>2.6</td>
<td>0.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>0.6</td>
<td>6.2</td>
<td>0.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.3</td>
<td>2.7</td>
<td>0.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Ovaries</td>
<td>1.2</td>
<td>12.2</td>
<td>1.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Testes</td>
<td>0.3</td>
<td>3.1</td>
<td>0.3</td>
<td>3.4</td>
</tr>
</tbody>
</table>
Red Marrow        0.5  4.6  0.5  4.4
Urinary Bladder Wall  1.5  15.5  3.0  30.0
Total Body       0.4  4.2  0.4  4.2

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.

2.3 Instructions for Preparation

Preparation of the Technetium Tc 99m Sestamibi from the Kit for Preparation of Technetium Tc 99m Sestamibi Injection is done by the following aseptic procedure:

Boiling Water Bath Procedure:

a. Prior to adding the Sodium Pertechnetate Tc 99m Injection to the vial, inspect the vial carefully for the presence of damage, particularly cracks, and do not use the vial if found. Tear off a radiation 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.

c. Place the vial in a suitable radiation shield with a fitted radiation cap.

d. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc 99m Injection [925-5550 MBq, (25–150 mCi)] in approximately 1 to 3 mL.

e. Aseptically add the Sodium Pertechnetate Tc 99m Injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.

f. Shake vigorously, about 5 to 10 quick upward-downward motions.

g. Remove the vial from the lead shield and place upright in 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 crimp.

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

i. Using proper shielding, the vial 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 Tc 99m concentration, total volume, assay time and date, expiration time and lot number on the vial shield label and affix the label to the shield.

k. Store the reaction vial containing the Technetium Tc 99m Sestamibi at 15° to 25°C until use; at such time the product should be aseptically withdrawn. Technetium Tc 99m Sestamibi should be used within six hours of preparation. The vial contains no preservative.

Note: Adherence to the above product reconstitution instructions is recommended.

Cardinal Health 414, LLC's Kit for the Preparation of Technetium Tc 99m Sestamibi Injection is not to be used with the Recon-o-Stat™ thermal cycler due to the smaller vial size requirements of this heating device.

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 Tc 99m Sestamibi

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 B-F, pre-cut to 2.5 cm x 7.5 cm.
2. Dry the plate or plates at 100°C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.
3. Apply 1 drop of ethanol\(^1\) using a 1 mL syringe with a 22–26 gauge needle, 1.5 cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY.
4. Add 2 drops of Technetium Tc 99m Sestamibi solution, side by side on top of the ethanol\(^1\) spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).
5. The TLC tank is prepared by pouring ethanol\(^1\) to a depth of 3-4 mm. Cover the tank and let it equilibrate for ~10 minutes.
6. Develop the plate in the covered TLC tank in ethanol\(^1\) for a distance of 5 cm from the point of application.
7. Cut the TLC plate 4 cm from the bottom and measure the Tc 99m activity in each piece by appropriate radiation detector.
8. Calculate the % Tc 99m Sestamibi as:

\[
\% \text{Tc } 99\text{m Sestamibi} = \frac{\mu\text{Ci Top Piece}}{\mu\text{Ci Both Pieces}} \times 100
\]

\(^{1}\)The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99%) should remain at ≥ 95% ethanol content for one week after opening if stored tightly capped, in a cool dry place.

3 DOSAGE FORMS AND STRENGTHS
Kit for Preparation of Technetium Tc 99m Sestamibi 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 continuous monitoring and treatment in accordance with safe, accepted clinical procedure. Infrequently, death has occurred 4 to 24 hours after Tc 99m Sestamibi use and is usually associated with exercise stress testing [see Warnings and Precautions (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 Tc 99m 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 Tc 99m Sestamibi imaging. Patients who receive Technetium Tc 99m Sestamibi for either myocardial or breast imaging are receiving the same drug. Caution should be exercised and emergency equipment should be available when administering Technetium Tc 99m Sestamibi. Also, before administering Technetium Tc 99m Sestamibi Injection, patients should be asked about the possibility of allergic reactions to the drug.

5.2 General Precautions
The contents of the vial are intended only for use in the preparation of Technetium Tc 99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

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 Tc 99m 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 Tc 99m labeling reactions depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc 99m Injection containing oxidants should not be used.

Technetium Tc 99m 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 exercise stress test endpoints sufficient to stop the test reported during controlled studies (two-thirds were cardiac patients) were:
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 Warnings and Precautions (5)]. Adverse events reported at a rate of 0.5% or greater after receiving Technetium Tc 99m Sestamibi administration are shown in the following table:

Table 2 Selected Adverse Events Reported in > 0.5% of Patients Who Received Technetium Tc 99m Sestamibi in Either Breast or Cardiac Clinical Studies*

<table>
<thead>
<tr>
<th>Body System</th>
<th>Breast Studies</th>
<th>Cardiac Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women n = 673</td>
<td>Women n = 685</td>
</tr>
<tr>
<td></td>
<td>Men n = 2361</td>
<td>Total n = 3046</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21 (3.1%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>11 (1.6%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Chest Pain/Angina</td>
<td>9 (1.3%)</td>
<td>24 (3.5%)</td>
</tr>
<tr>
<td>ST segment changes</td>
<td>0 (0%)</td>
<td>18 (2.6%)</td>
</tr>
<tr>
<td>Digestive System</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 Perversion</td>
<td>129 (19.2%)</td>
<td>60 (8.8%)</td>
</tr>
<tr>
<td>Parosmia</td>
<td>8 (1.2%)</td>
<td>6 (0.9%)</td>
</tr>
</tbody>
</table>

* Excludes the 22 patients whose genders were not recorded.

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

The following adverse reactions have been reported in ≤ 0.5% of patients: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis; angioedema, arrhythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthenia, and vomiting within two hours after a second injection of Technetium Tc 99m Sestamibi. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, pruritus, 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
Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Sestamibi. It is also not known whether Technetium Tc 99m Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc 99m Sestamibi should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers
Technetium Tc 99m Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium Tc 99m Sestamibi is excreted in human milk. Therefore, formula feedings should be substituted for breast feedings.

8.4 Pediatric Use
Safety and effectiveness in the pediatric population have not been established.

No evidence of diagnostic efficacy or clinical utility of Technetium Tc 99m Sestamibi 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 Technetium Tc 99m Sestamibi 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, CABG or coronary angioplasty. The standard of truth was defined as cardiac events occurring 6 months following the administration of Technetium Tc 99m Sestamibi. 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 Technetium Tc 99m Sestamibi myocardial perfusion imaging and who had coronary angiography within three months of the Technetium Tc 99m Sestamibi scan was designed to measure sensitivity and specificity of Technetium Tc 99m Sestamibi scan. Out of 72 patients who had both evaluable Technetium Tc 99m Sestamibi scans and evaluable angiographic images, only one patient had both an abnormal angiogram and an abnormal Technetium Tc 99m Sestamibi 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 Technetium Tc 99m Sestamibi 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 Clinical Pharmacology (12)].

The radiation absorbed doses in adolescents, both at rest and stress, were similar to those observed in adults [see Dosage and Administration (2.2)]. 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 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 the type of the adverse events were similar to the ones observed in the studies of Technetium Tc 99m Sestamibi in adults. Two of the 609 had a serious adverse event: one
patient received a Technetium Tc 99m Sestamibi overdose but remained asymptomatic, and one patient had an asthma exacerbation following administration.

8.5 Geriatric Use
Of 3068 patients in clinical studies of Technetium Tc 99m Sestamibi for myocardial imaging, 693 patients were 65 or older and 121 were 75 or older.

Of 673 patients in clinical studies of Technetium Tc 99m Sestamibi for breast imaging, 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 Technetium Tc 99m Sestamibi 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
- Mannitol - 20 mg
- Stannous Chloride, Dihydrate, minimum (SnCl₂•2H₂O) - 0.025 mg
- Stannous Chloride, Dihydrate (SnCl₂•2H₂O) - 0.075 mg
- Tin Chloride (stannous and stannic) Dihydrate, 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 Tc 99m Injection. 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 Tc 99m[MIBI]₆⁺ where MIBI is 2-methoxy isobutyl isonitrile.

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate has the following structural
11.1 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours\(^2\). Photons that are useful for detection and imaging studies are listed below in Table 3.

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Mean %/Disintegration</th>
<th>Mean Energy (KeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma -2</td>
<td>89.07</td>
<td>140.5</td>
</tr>
</tbody>
</table>


11.2 External Radiation

The specific gamma ray constant for Tc 99m is 5.4 microcoulombs/Kg-MBq-hr (0.78R/mCi-hr) at 1 cm. The first half value layer is 0.017 cm of Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 4. To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of 1,000.

<table>
<thead>
<tr>
<th>Shield Thickness (Pb) cm</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.017</td>
<td>0.5</td>
</tr>
<tr>
<td>0.08</td>
<td>(10^{-1})</td>
</tr>
<tr>
<td>0.16</td>
<td>(10^{-2})</td>
</tr>
<tr>
<td>0.25</td>
<td>(10^{-3})</td>
</tr>
<tr>
<td>0.33</td>
<td>(10^{-4})</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Hours</th>
<th>Fraction Remaining</th>
<th>Hours</th>
<th>Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>1.000</td>
<td>7</td>
<td>0.447</td>
</tr>
<tr>
<td>1</td>
<td>0.891</td>
<td>8</td>
<td>0.398</td>
</tr>
<tr>
<td>2</td>
<td>0.794</td>
<td>9</td>
<td>0.355</td>
</tr>
<tr>
<td>3</td>
<td>0.708</td>
<td>10</td>
<td>0.316</td>
</tr>
<tr>
<td>4</td>
<td>0.631</td>
<td>11</td>
<td>0.282</td>
</tr>
<tr>
<td>5</td>
<td>0.562</td>
<td>12</td>
<td>0.251</td>
</tr>
<tr>
<td>6</td>
<td>0.501</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Calibration Time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Technetium Tc 99m Sestamibi is a cationic Tc 99m 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 Tc 99m 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 Tc 99m 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 clearing component clears with a $t_{1/2}$ of 4.3 minutes at rest, and clears with a $t_{1/2}$ 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 Tc 99m 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 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 illustrates the biological clearance as well as effective clearance (which includes biological clearance and radionuclide decay) of Tc 99m Sestamibi from the heart and liver.

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

Table 6 Biological and Effective Clearance

<table>
<thead>
<tr>
<th></th>
<th>Heart REST</th>
<th>Liver</th>
<th>Heart STRESS</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Biological</td>
<td>Effective</td>
<td>Biological</td>
<td>Effective</td>
</tr>
<tr>
<td>5 min.</td>
<td>1.2</td>
<td>1.2</td>
<td>19.6</td>
<td>19.4</td>
</tr>
<tr>
<td>30 min.</td>
<td>1.1</td>
<td>1.0</td>
<td>12.2</td>
<td>11.5</td>
</tr>
<tr>
<td>1 hour</td>
<td>1.0</td>
<td>0.9</td>
<td>5.6</td>
<td>5.0</td>
</tr>
<tr>
<td>2 hours</td>
<td>1.0</td>
<td>0.8</td>
<td>2.2</td>
<td>1.7</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.8</td>
<td>0.5</td>
<td>0.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

A study in a dog myocardial ischemia model reported that Technetium Tc 99m 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. Definitive human studies to demonstrate possible redistribution have not been reported. In patients with documented myocardial infarction, imaging revealed the infarct up to four hours post dose.

Metabolism

The agent is excreted without any evidence of metabolism.

Elimination

The major pathway for clearance of Tc 99m 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 Dosage and Administration (2.2)].

The active intermediate, Cu(MIBI)\textsubscript{4}BF\textsubscript{4}, was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and sister chromatid exchange tests (all in vitro). At cytotoxic concentrations (> 20 µg/mL), an increase in cells with chromosome aberrations was observed in the in vitro human lymphocyte assay. Cu(MIBI)\textsubscript{4}BF\textsubscript{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 × maximal human dose).

14 CLINICAL STUDIES

CLINICAL TRIALS:

MYOCARDIAL IMAGING: In a trial of rest and stress Technetium Tc 99m Sestamibi 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 Technetium Tc 99m Sestamibi 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, 24/521 (4.6%) had a cardiac event.

Table 7 Cardiac Events

<table>
<thead>
<tr>
<th>Baseline Scan</th>
<th>Proportion of patients with events by scan results*</th>
<th>Proportion of scan result in patients with events; N=24*</th>
<th>Proportion of event-free patients by scan results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1/206 (0.5%)</td>
<td>1/24 (4.2%)</td>
<td>205/206 (99.5%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>23/315 (7.3%)†</td>
<td>23/24 (95.8%)†</td>
<td>292/315 (92.7%)†</td>
</tr>
</tbody>
</table>

* Note: Similar findings were found in two studies with patients who had pharmacologic stress Technetium Tc 99m Sestamibi imaging.
† p<0.01

Although patients with normal images had a lower cardiac event rate than those with abnormal images, in all patients with abnormal images it was not possible to predict which patient would be likely to have further cardiac events; i.e., such individuals were not distinguishable from other patients with abnormal images.

The findings were not evaluated for defect location, disease duration, specific vessel involvement or intervening management.

In earlier trials, using a template consisting of the anterior wall, inferior-posterior wall and isolated apex, localization in the anterior or inferior-posterior wall in patients with suspected angina or coronary artery disease was shown. Disease localization isolated to the apex has not been established. Tc 99m Sestamibi has not been studied or evaluated in cardiac disorders other than coronary artery disease.

BREAST IMAGING: Technetium Tc 99m Sestamibi was evaluated in two 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) palpable breast lesion (study B, n=286, mean age = 50 years). In both studies all patients were scheduled for biopsy.

Technetium Tc 99m Sestamibi (20–30 mCi) was injected intravenously in a vein that was contralateral to the breast lesion in question. Planar imaging was completed with a high resolution collimator with a 10% window centered at 140 keV, and 128 x 128 matrix. An initial marker image, that was not used in the data analysis, was obtained using a cobalt Co57 point source as a marker of a palpable mass. Images were obtained 5 minutes after injection as follows: lateral image of the affected breast for 10 minutes, lateral image of the contralateral breast for 10 minutes, and an anterior image of both breasts for 10 minutes. For the lateral image the patients were positioned in a prone position. For the anterior image, the patients were supine. The Technetium Tc 99m Sestamibi scintigraphic images were read in a randomized method by two groups of three blinded readers. Technetium Tc 99m Sestamibi uptake was scored as: normal (no uptake), equivocal, low, moderate, or high uptake. The results of Technetium Tc 99m Sestamibi images and mammography were analyzed in comparison to histopathologic findings of malignant or non-malignant disease.

As shown in Table 8 for the 483 evaluable patients, the sensitivity and specificity of any degree of Technetium Tc 99m Sestamibi uptake appear to vary with the presence or absence of palpable mass.

Table 8 Overall Technetium Tc 99m Sestamibi Blinded Results of Target Lesions * Identified at
In separate retrospective subset analyses of 259 patients with dense (heterogeneously/extremely dense) and 275 patients with fatty (almost entirely fat/numerous vague densities) breast tissue, the Technetium Tc 99m Sestamibi results were similar. Overall, the studies were not designed to compare the performance of Technetium Tc 99m Sestamibi with the performance of mammography in patients with breast densities or other coexistent breast tissue disorders.

In general the histology seems to correlate with the degree of Technetium Tc 99m Sestamibi uptake. As shown in Table 9 and Table 10, the majority of the normal Technetium Tc 99m Sestamibi images are associated with non-malignant tissue (78–81%) and the majority of low, moderate or high uptake Technetium Tc 99m Sestamibi images are associated with malignant disease (79–83%). In an individual patient, however, the intensity of Technetium Tc 99m Sestamibi uptake can not be used to confirm the presence or absence of malignancy. Equivocal results do not have a correlation with histology.

**Table 9 Degree of Technetium Tc 99m Sestamibi Breast Imaging Uptake in Comparison to Histopathology Results in Patients with Mammographically Detected Non-Palpable Lesions**

<table>
<thead>
<tr>
<th>Uptake</th>
<th>Normal Uptake N = 249 lesions</th>
<th>Equivocal Uptake N = 25 lesions</th>
<th>Low, Moderate or High Uptake N = 66 lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-malignant†</td>
<td>201 (81%)</td>
<td>14 (56%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>48 (19%)</td>
<td>11 (44%)</td>
<td>52 (79%)</td>
</tr>
</tbody>
</table>

* Median finding for 3 blinded readers
† Includes benign tissue, fibroadenoma, benign intramammary nodes, radial scar.
An estimate of the likelihood of malignancy based on Technetium Tc 99m Sestamibi 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 Technetium Tc 99m Sestamibi 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. Technetium Tc 99m Sestamibi uptake can occur in both benign and malignant disease. THE CLINICAL USEFULNESS OF A POSITIVE TECHNETIUM Tc 99m SESTAMIBI IMAGE IN THE ABSENCE OF AN ABNORMAL MAMMOGRAM OR A PALPABLE LESION IS NOT KNOWN.

15 REFERENCES
Not applicable.

16 HOW SUPPLIED/STORAGE AND HANDLING
Kit for Preparation of Technetium Tc 99m Sestamibi Injection is supplied as a 5 mL vial in kits of twenty (20) vials (NDC # 65857-500-20), 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 lyophilized and stored under nitrogen. Store at 15-25°C (59-77°F) before and after reconstitution.

Kit for Preparation of Technetium Tc 99m Sestamibi Injection contains no preservatives. 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 by the U.S. Nuclear Regulatory Commission to use byproduct material identified in 10 CFR 35.200 or under an equivalent license issued by an Agreement State or Licensing State.

17 PATIENT COUNSELING INFORMATION
CARDIOLITE® and MIRALUMA® are different names for the same drug (Kit for Preparation of Technetium Tc 99m Sestamibi Injection). 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.

CARDIOLITE®, MIRALUMA®, and Recon-o-Stat™ are trademarks of Lantheus Medical Imaging, Inc.

Distributed by:
Cardinal Health 414, LLC
7000 Cardinal Place
Dublin, OH 43017

Revised June 2018
Lymphoseek (technetium Tc 99m tilmanocept) injection, for subcutaneous, intradermal, subareolar, or peritumoral use

Initial U.S. Approval: 2013

---

**INDICATIONS AND USAGE**

Lymphoseek is a radioactive diagnostic agent indicated with or without scintigraphic imaging for:

- Lymphatic mapping using a handheld gamma counter to locate lymph nodes draining a primary tumor site in patients with solid tumors for which this procedure is a component of intraoperative management. (1)
- Guiding sentinel lymph node biopsy using a handheld gamma counter in patients with clinically node negative squamous cell carcinoma of the oral cavity, breast cancer or melanoma. (1)

---

**DOSAGE AND ADMINISTRATION**

- Lymphoseek is supplied as a Kit and must be prepared by radiolabeling with technetium Tc 99m and diluting with the supplied diluent or pharmacy-available sterile 0.9% sodium chloride injection prior to use. (2.3)
- Use aseptic technique and radiation safety precautions during Lymphoseek preparation and handling. Determine the total injection volume and number of sites to be injected for each patient before preparing Lymphoseek. (2.1, 2.3)
- Recommended dose of Lymphoseek is 18.5 MBq (0.5 mCi) administered at least 15 minutes before initiating intraoperative lymphatic mapping or sentinel node biopsy procedures: complete these procedures within 15 hours of Lymphoseek injection. (2.2, 2.3)
- Recommended routes of administration are intradermal, subcutaneous, subareolar, or peritumoral. (2.3)
- Use radiolabeled Lymphoseek within 6 hours of its preparation. (2.3)

---

**DOSE FORMS AND STRENGTHS**

The Kit for preparation of Lymphoseek contains five Tilmanocept Powder vials each containing 250 mcg tilmanocept, and is packaged either with or without five DILUENT for Lymphoseek vials each containing 4.5 mL of sterile buffered saline with phenol. After radiolabeling with technetium Tc 99m and dilution, Lymphoseek contains approximately 92.5 MBq (2.5 mCi) and 250 mcg of technetium Tc 99m tilmanocept in 0.5 mL to 5 mL total volume for injection. (3)

---

**CONTRAINDICATIONS**

None. (4)

---

**WARNINGS AND PRECAUTIONS**

- Hypersensitivity: Ask patients about prior reactions to drugs, especially dextran or modified forms of dextran. Observe for hypersensitivity signs and symptoms following Lymphoseek injection. Have resuscitation equipment and trained personnel immediately available. (5.1)

---

**ADVERSE REACTIONS**

The most common adverse reactions (incidence < 1%) are injection site irritation and/or pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cardinal Health at 1-800-618-2768 or www.lymphoseek.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---

**USE IN SPECIFIC POPULATIONS**

Lactation. To decrease radiation exposure to the breastfed infant, advise a lactating woman to pump and discard breast milk after the administration of Lymphoseek for 24 hours. (8.2)

---

See 17 for PATIENT COUNSELING INFORMATION

---

**FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATION AND USAGE
2 DOSAGE AND ADMINISTRATION

---

**FULL PRESCRIBING INFORMATION**

Revised: 06/2019
**Route of Administration and Injection Method**

The route of administration depends on the tumor location and the planned injection technique and includes: subcutaneous, intradermal, subareolar, or peritumoral injection.

Lymphoseek may be administered to a patient as a single injection or as multiple injections. The recommended total injection volume for each patient (Table 1) is 0.1 mL administered in a single syringe; 0.5 mL administered in a single syringe or in multiple syringes (0.1 mL to 0.25 mL each); or 1 mL administered in multiple syringes (0.2 mL to 0.5 mL each).

The lymphatic system architecture and function may be changed by prior surgery, radiation, edema, inflammation or metastatic disease, and may result in changes to lymph node localization by a radiopharmaceutical or other tracers, including colorimetric agents. Avoid injections into biopsy wound areas that show evidence of edema or inflammation.

In animal studies, locally injected anesthetics have been reported to reduce lymphatic flow. Concomitant administration of local anesthetics with Lymphoseek is not recommended and may impair the lymph nodal mapping.

### 2.3 Drug Preparation

**General Considerations**

- Kit for the preparation of Lymphoseek contains five Tilmanocept Powder vials, each containing 250 mcg of tilmanocept from which 50 mcg is intended for administration to a patient.
  - The Kit for the preparation of Lymphoseek is packaged either with or without five DILUENT for Lymphoseek vials each containing 4.5 mL of sterile buffered saline with phenol.
  - The Kit for the preparation of Lymphoseek may also be diluted with pharmacy-available sterile 0.9% sodium chloride injection.
- A diluent is used to dilute Lymphoseek after the radiolabeling procedure. The amount of diluent used varies, depending on the total injection volume and the number of syringes used for each patient.
- The vial components of the Kit for the preparation of Lymphoseek are intended solely for use in the preparation of Lymphoseek. Do not administer the unprepared vial components of the Kit directly to a patient.
- Follow aseptic procedures during preparation and administration.

**Drug Preparation Instructions**

Prior to preparation of Lymphoseek, determine the planned injection technique and the number of injections that will be used for a given patient. For each injection prepare a separate syringe. Based on the planned number of injection syringes and the planned total injection volume per patient, determine (from Table 1 below) the Reconstituted Vial Volume of radiolabeled Lymphoseek.

**Table 1. Preparation of Lymphoseek for Administration**

<table>
<thead>
<tr>
<th>Planned Number of Injections for a Patient</th>
<th>Total Injection Volume Per Patient</th>
<th>Reconstituted Vial Volume of Radiolabeled Lymphoseek</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 syringe x 0.1 mL</td>
<td>0.1 mL</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>5 syringes x 0.1 mL, or 2 syringes x 0.25 mL or 1 syringe x 0.5 mL</td>
<td>0.5 mL</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>5 syringes x 0.2 mL, or 4 syringes x 0.25 mL or 2 syringes x 0.5 mL</td>
<td>1 mL</td>
<td>5 mL</td>
</tr>
</tbody>
</table>

Once the Reconstituted Vial Volume is established, use the following steps to prepare radiolabeled Lymphoseek:

**Radiolabeling**

- Inspect the Tilmanocept Powder vial for any damage. Do not use if vial integrity appears compromised. Do not vent the Tilmanocept Powder vial prior to or during radiolabeling.
- Use Technetium Tc 99m pertechnetate, sodium injection solution from a technetium Tc 99m generator within 8 hours of its elution.
- Use a sterile syringe, aseptically draw approximately 92.5 MBq (2.5 mCi) of Technetium Tc 99m pertechnetate sodium injection solution in either about 0.35 mL volume (for 0.5 mL Reconstituted Vial Volume) or about 0.7 mL volume (for 2.5 mL or 5 mL Reconstituted Vial Volume). Assay the syringe for technetium Tc 99m activity in a dose calibrator.
- Write the radioactivity amount, the Reconstituted Vial Volume, date and time, expiration time and lot number in the space provided on the radioactive product vial label and affix it to the Tilmanocept Powder vial. Place the vial in a radiation shield and sanitize the septum with alcohol wipe.
- Aseptically add Technetium Tc 99m pertechnetate, sodium injection solution to the Tilmanocept Powder vial. Without withdrawing the needle, remove an equal volume of headspace gas. Do not vent.
- Remove the needle, gently shake the vial to mix the contents, and then let it stand at room temperature for at least 15 minutes.

**Reconstitution**

- Assay the reconstituted vial for total radioactivity using a dose calibrator. Write the technetium Tc 99m activity concentration, total volume, assay time and date, expiration time, and lot number on the shield label supplied with the Kit. Affix the label to the shield.
- Determine the radiochemical purity of the radiolabeled product [see Dosage and Administration (2.4)]. Do not use if the radiochemical purity is less than 90%.
- Withdraw the required volume of the radiolabeled product into the required number of syringes. Assay the syringe(s) in a dose calibrator. Write the radioactivity amount, date and time of assay, volume, and expiration time (this is not to exceed 6 hours from preparation time) on the supplied syringe label and affix it to the syringe(s).

**Duration of Use and Storage of Radiolabeled Solution**

- Store the radiolabeled Lymphoseek in radiation shielding at room temperature.
- Use the radiolabeled Lymphoseek within 6 hours of preparation. Discard the unused radiolabeled Lymphoseek.

**2.4 Determination of Radiochemical Purity of Radiolabeled Lymphoseek**

Determine radiochemical purity of the reconstituted radiolabeled Lymphoseek by Instant Thin Layer Chromatography (ITLC) using either Whatman Grade 1, 3MM, 31ET Chr or Biodex 150-001 Red Strips (cellulose chromatography paper) using the following method:
a. Mark the chromatographic strip for origin, mid and solvent front lines with a pencil as shown below:

![Chromatography Strip Diagram]

b. Apply a small drop (3 - 10 microliters) of the reconstituted product at the center of the origin line chromatography strip. Let the product spot dry.

c. Place the strip into a chromatography chamber containing 1 mL of acetone as the developing solvent. Allow the solvent to migrate to the solvent front line (5 cm from the bottom of the Whatman strips and 3.5 cm for the Biodex strip). Remove the strip from the chamber, let it dry and cut it in half. Count each half of the strip with a suitable radioactivity counting apparatus (dose calibrator or multichannel analyzer).

d. Calculate the percent radiochemical purity (% RCP) as follows:

\[
% \text{ RCP} = \frac{\text{Counts (activity) in bottom half}}{\text{Counts (activity) in bottom half} + \text{Counts (activity) in top half}} \times 100
\]

e. Do not use the reconstituted Lymphoseek if the radiochemical purity is less than 90%.

2.5 Lymphatic Mapping and Sentinel Lymph Node Biopsy Following Injection of Lymphoseek

- Lymphoscintigraphy may be used to assist in planning the lymph node mapping procedures. In clinical studies, preoperative scintigraphic imaging was performed using planar imaging techniques and/or SPECT/CT to establish a map of nodal basins and to facilitate intraoperative identification of lymph nodes. Imaging was performed as early as immediately after injection and up to 21 hours [see Clinical Studies (14)].

- Use a handheld gamma counter to identify nodes that concentrated the injected radioactivity.

- For intraoperative lymphatic mapping, first measure the background radioactivity counts from tissue at least 20 centimeters distal to the injection site. The three sigma threshold (background radioactivity counts plus three times the square root of the mean background count) may be used as an estimate of the threshold for positive localization of Lymphoseek, as exemplified in Table 2.

2.6 Radiation Dosimetry

The radiation doses to organs and tissues of a patient weighing 70 kg given 18.5 MBq (0.5 mCi) of Lymphoseek are shown in Table 3.

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Breast Cancera mGy (rad)</th>
<th>Melanoma b mGy (rad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>brain</td>
<td>0.003 (0.0003)</td>
<td>0.0927 (0.0093)</td>
</tr>
<tr>
<td>breast (injection site)</td>
<td>1.659 (0.1659)</td>
<td>0.7903 (0.079)</td>
</tr>
<tr>
<td>gall bladder wall</td>
<td>0.0349 (0.0035)</td>
<td>0.0712 (0.0071)</td>
</tr>
<tr>
<td>lower large intestine wall</td>
<td>0.0123 (0.0012)</td>
<td>0.057 (0.0057)</td>
</tr>
<tr>
<td>small intestine</td>
<td>0.0101 (0.001)</td>
<td>0.0594 (0.0059)</td>
</tr>
<tr>
<td>stomach</td>
<td>0.0184 (0.0018)</td>
<td>0.0562 (0.0056)</td>
</tr>
<tr>
<td>upper large intestine wall</td>
<td>0.0125 (0.0012)</td>
<td>0.0582 (0.0058)</td>
</tr>
<tr>
<td>kidney</td>
<td>0.1863 (0.0186)</td>
<td>0.278 (0.0278)</td>
</tr>
<tr>
<td>liver</td>
<td>0.0324 (0.0032)</td>
<td>0.0929 (0.0093)</td>
</tr>
<tr>
<td>lungs</td>
<td>0.0374 (0.0037)</td>
<td>0.0599 (0.006)</td>
</tr>
<tr>
<td>muscle</td>
<td>0.0092 (0.0009)</td>
<td>0.0451 (0.0045)</td>
</tr>
<tr>
<td>ovaries</td>
<td>0.187 (0.0187)</td>
<td>0.2991 (0.0299)</td>
</tr>
<tr>
<td>red marrow</td>
<td>0.0127 (0.0013)</td>
<td>0.0507 (0.0051)</td>
</tr>
<tr>
<td>bone</td>
<td>0.0177 (0.0018)</td>
<td>0.0878 (0.0088)</td>
</tr>
<tr>
<td>spleen</td>
<td>0.0285 (0.0029)</td>
<td>0.0598 (0.006)</td>
</tr>
<tr>
<td>testes</td>
<td>0.0501 (0.005)</td>
<td>0.1043 (0.0104)</td>
</tr>
<tr>
<td>thymus</td>
<td>0.1168 (0.0117)</td>
<td>0.0577 (0.0058)</td>
</tr>
<tr>
<td>thyroid</td>
<td>0.088 (0.0088)</td>
<td>0.0464 (0.0046)</td>
</tr>
<tr>
<td>urinary bladder</td>
<td>0.0586 (0.0059)</td>
<td>0.1401 (0.014)</td>
</tr>
<tr>
<td>total body</td>
<td>0.0195 (0.0019)</td>
<td>0.0547 (0.0055)</td>
</tr>
</tbody>
</table>

Effective Dose Equivalent

- **males**: 296 microSv
- **females**: 330.2 microSv

- **males**: 202.4 microSv
- **females**: 251.1 microSv

a Calculated from data of 18 patients with breast cancer who received four peritumoral injections of 4 mcg, 20 mcg, and 100 mcg doses of Lymphoseek.

b Calculated from data of 18 patients with melanoma who received four intradermal injections of 20 mcg, 100 mcg, and 200 mcg doses of Lymphoseek. Due to the differences in injection sites among patients with melanoma, the injection site was assumed to be the breast for the purposes of this calculation, as it represents the nearest anatomical construct for the skin from the anatomical sites appropriately included in the estimates.

3 DOSAGE FORMS AND STRENGTHS

The Kit for preparation of Lymphoseek (technetium Tc 99m tilmanocept) injection is supplied as five Tilmanocept Powder vials each containing 250 mcg tilmanocept, and is packaged either with or without five DILUENT for Lymphoseek vials each containing 4.5 mL of sterile buffered saline with phenol. After radiolabeling with technetium Tc 99m, Lymphoseek contains approximately 92.5 MBq (2.5 mCi) and 250 mcg technetium Tc 99m tilmanocept in 0.5 mL to 5 mL total volume.
4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Lymphoseek may pose a risk of hypersensitivity reactions due to its chemical similarity to dextran [see Description (11)]. Serious hypersensitivity reactions have been associated with dextran and modified forms of dextran (such as iron dextran drugs).

Before administering Lymphoseek, ask patients about prior hypersensitivity reactions to drugs, especially to dextran and modified forms of dextran. Have resuscitation equipment and trained personnel immediately available at the time of Lymphoseek administration.

5.2 Radiation Risks
Any radiation-emitting product may increase the risk for cancer, especially in pediatric patients. Adhere to the dose recommendations and ensure safe handling to minimize the risk for excessive radiation exposure to either patients or health care workers.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In open label, single arm clinical trials, 553 patients with either breast cancer, melanoma, or squamous cell carcinoma of the oral cavity, skin, and lip received Lymphoseek. No patients experienced serious adverse reactions. Injection site irritation (4 patients; 0.7%) and pain (1 patient; 0.2%) were reported.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Lymphoseek use in pregnant women. Additionally, animal reproduction studies have not been conducted with technetium Tc 99m tilmanocept. However, all radiopharmaceuticals, including Lymphoseek, have a potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering Lymphoseek administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from the drug and the gestational timing of exposure.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively, regardless of drug exposure.

8.2 Lactation
Risk Summary
No data are available regarding the presence of technetium Tc 99m tilmanocept in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Exposure of Lymphoseek to a breastfed infant can be minimized by temporary discontinuation of breastfeeding [see Clinical Considerations]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Lymphoseek and any potential adverse effects on the breastfed child from Lymphoseek or from the underlying maternal condition.

Clinical Considerations
To decrease radiation exposure to the breastfed infant, advise a lactating woman to pump and discard breast milk after the administration of Lymphoseek for 24 hours, in order to minimize radiation to a breastfed child.

8.4 Pediatric Use
Safety and effectiveness of Lymphoseek in patients less than 18 years of age have not been established.

8.5 Geriatric Use
Of the 553 patients enrolled in clinical studies of breast cancer, melanoma, and squamous cell carcinoma (SCC) of oral cavity, skin, and lip, 179 (32%) were aged 65 or older. Review of the clinical data, including evaluation of the frequency of adverse reactions, has not identified differences in safety or efficacy between elderly patients 65 to 90 years of age and younger patients 18 to 65 years of age.

11 DESCRIPTION

Chemical Characteristics
The active ingredient in Lymphoseek, a radioactive diagnostic agent, is technetium Tc 99m tilmanocept. Technetium Tc 99m binds to the diethylenetriaminepentaacetic acid (DTPA) moieties of the tilmanocept molecule.

- The molecular formula of technetium Tc 99m tilmanocept is \([C_{29}H_{28}N_{9}O_{9}S^{99mTc}]_n\). It contains 3-8 conjugated DTPA (diethylenetriaminepentaacetic acid) molecules (b); 12-20 conjugated mannose molecules (c) with 0-17 amine side chains (a) remaining free.
- The calculated average molecular weight of tilmanocept ranges from 15,281 to 23,454 g/mol.
- Technetium Tc 99m tilmanocept has the following structural formula:

Lymphoseek (technetium Tc 99m tilmanocept) injection is supplied as a Kit which contains five Tilmanocept Powder vials. Each Tilmanocept Powder vial contains the non-radioactive ingredients needed to produce technetium Tc 99m tilmanocept. The vial contains a sterile, non-pyrogenic, white to off-white lyophilized powder that consists of a mixture of 250 mcg tilmanocept, 20 mg trehalose dihydrate, 0.5 mg glycine, 0.5 mg sodium ascorbate, and 0.075 mg stannous chloride dihydrate.

The DILUENT for Lymphoseek contains 4.5 mL sterile buffered saline consisting of 0.04% (w/v) potassium phosphate, 0.11% (w/v) sodium phosphate (heptahydrate), 0.5% (w/v) sodium chloride, and 0.4% (w/v) phenol.
Physical Characteristics
Technetium Tc 99m decays by isomeric transition with a physical half-life of approximately 6 hours. The principal photon that is useful for detection and imaging studies is listed in Table 4.

Table 4. Principal Radiation Emission Data

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Mean % Disintegration</th>
<th>Mean Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma-2</td>
<td>89.1</td>
<td>140.5</td>
</tr>
</tbody>
</table>


External Radiation
The linear mass energy absorption attenuation coefficient for Tc 99m is 18.9 cm⁻¹. The first half-value layer is 0.037 cm of lead (Pb). The use of a 0.25 cm thick standard radiation lead shield will attenuate the radiation emitted by millicurie amounts of technetium Tc 99m by a factor of about 100. A range of values for the relative attenuation of the radiation of technetium Tc 99m that results with various thicknesses of lead shielding are displayed in Table 5.

Table 5. Radiation Attenuation by Lead Shielding

<table>
<thead>
<tr>
<th>Shield Thickness, cm of lead (Pb)</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.037</td>
<td>0.5</td>
</tr>
<tr>
<td>0.12</td>
<td>10⁻¹</td>
</tr>
<tr>
<td>0.24</td>
<td>10⁻²</td>
</tr>
<tr>
<td>0.36</td>
<td>10⁻³</td>
</tr>
<tr>
<td>0.49</td>
<td>10⁻⁴</td>
</tr>
</tbody>
</table>

To correct for physical decay of the radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 6.

Table 6. Physical Decay Chart; Tc 99m, Half-Life of approximately 6 Hours

<table>
<thead>
<tr>
<th>Hours</th>
<th>Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0.891</td>
</tr>
<tr>
<td>3</td>
<td>0.708</td>
</tr>
<tr>
<td>6</td>
<td>0.501</td>
</tr>
<tr>
<td>12</td>
<td>0.251</td>
</tr>
<tr>
<td>15</td>
<td>0.178</td>
</tr>
</tbody>
</table>

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Lymphoseek (technetium Tc 99m tilmanocept) is a radioactive diagnostic agent. It accumulates in lymphatic tissue and selectively binds to mannose binding receptors (CD206) located on the surface of macrophages and dendritic cells. Technetium Tc 99m tilmanocept is a macromolecule consisting of multiple units of diethyleneetriaminepentaacetic acid (DTPA) and mannose, each covalently attached to a 10 kDa dextran backbone. The mannose acts as a ligand for the receptor, and the DTPA serves as a chelating agent for labeling with technetium Tc 99m.

12.2 Pharmacodynamics
In in vitro studies, technetium Tc 99m tilmanocept exhibited binding to human mannose binding receptors with a primary binding site affinity of $K_d = 2.76 \times 10^{-11}$ M. In clinical studies, technetium Tc 99m tilmanocept has been detectable in lymph nodes within 10 minutes and up to 30 hours after injection.

12.3 Pharmacokinetics
In dose-ranging clinical studies, injection site clearance rates were similar across all Lymphoseek doses (4 to 200 mcg) with a mean elimination rate constant in the range of 0.222 to 0.396/hr, resulting in a drug half-life at the injection site of 1.8 to 3.1 hours. The amount of the accumulated radioactive dose in the liver, kidney, and bladder reached a maximum 1 hour post administration of Lymphoseek and was approximately 1% to 2% of the injected dose in each tissue.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to assess the carcinogenicity potential of tilmanocept have not been conducted. Tilmanocept was not mutagenic in vitro in the Ames bacterial mutation assay and in the in vitro mouse lymphoma test, and was negative in the in vivo micronucleus test in mice.

Studies on reproductive fertility have not been conducted.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies
The efficacy and safety of Lymphoseek were assessed in three open-label, multicenter, single arm trials of patients with melanoma, breast cancer, or squamous cell carcinoma (SCC) of the oral cavity, skin, and lip (Studies 1, 2, and 3). Prior to the lymph node mapping and sentinel lymph node biopsy procedures, patients had no known regional nodal or metastatic disease by standard clinical staging criteria.

- In Studies 1 and 2, Lymphoseek was evaluated in patients with breast cancer and melanoma. Diagnostic efficacy for lymphatic mapping was determined by the number of histology-confirmed lymph nodes detected by Lymphoseek and/or the blue dye comparator. Lymphoseek was injected into patients at least 15 minutes prior to initiating lymphatic mapping procedures, and preoperative scintigraphic imaging was performed in 91% of patients. Separately, blue dye was injected shortly prior to initiation of the surgery. Lymphatic mapping was performed intraoperatively using a handheld gamma detection probe followed by excision of lymph nodes identified by Lymphoseek, blue dye, or the surgeon’s visual and palpation examination. The resected lymph nodes were evaluated by histopathology. Lymphoseek localization rate in pathologically-positive lymph nodes was also determined.

  - In Study 1, of 179 patients who received Lymphoseek, 94 (53%) had known or suspected breast cancer and 85 (47%) had known or suspected melanoma. The median age was 59 years (range 20 to 90 years) and most (72%) were women.

  - In Study 2, of 153 patients who received Lymphoseek, 77 (50%) had known or suspected breast cancer and 76 (50%) had known or suspected melanoma. The median age was 61 years (range 26 to 88 years) and most (68%) were women.

- In Study 3, Lymphoseek was evaluated primarily in patients with SCC of the oral cavity (T1-T4a, N0, M0). Diagnostic efficacy was determined by the patient level false negative rate of sentinel lymph node detection by Lymphoseek as confirmed by pathologic assessment of all lymph nodes removed during planned elective neck dissection (END). Lymphoseek was administered at least 15 minutes prior to the scheduled surgery, and preoperative scintigraphic imaging was performed in all patients. Lymphatic mapping was performed intraoperatively using a handheld gamma counter followed by excision of sentinel lymph nodes identified by Lymphoseek. Additional lymph nodes were removed during the END based upon tumor location and surgical practice. All resected lymph nodes (sentinel and non-sentinel) were evaluated for histopathology at the local site. Lymphoseek-identified nodes determined negative for cancer and melanoma. Diagnostic efficacy for lymphatic mapping was determined by the number of histologic-confirmed lymph nodes detected by Lymphoseek and/or the blue dye comparator. Lymphoseek was injected into patients at least 15 minutes prior to initiating lymphatic mapping procedures, and preoperative scintigraphic imaging was performed in 91% of patients. Separately, blue dye was injected shortly prior to initiation of the surgery. Lymphatic mapping was performed intraoperatively using a handheld detection probe followed by excision of lymph nodes identified by Lymphoseek, blue dye, or the surgeon’s visual and palpation examination. The resected lymph nodes were evaluated by histopathology. Lymphoseek localization rate in pathologically-positive lymph nodes was also determined.

  - Of the 85 patients who received Lymphoseek, 79 (93%) had intraoral SCC and 6 (7%) had cutaneous SCC. The median age was 59 years (range 23 to 87 years) and most (75%) were men.
14.2 Lymphoscintigraphy
An analysis of the three studies was performed to evaluate the agreement in location of lymph nodes identified by scintigraphic imaging and the handheld gamma counter. At least one scintigraphic “hot spot” was identified in 95% of patients imaged; the percentages were similar across tumor types. Overall, there was 84% agreement on a nodal level (when considering all missing observations as disagreement, as worst case scenario) between the location of preoperative scintigraphic imaging hot spots and the intraoperative lymph node findings (Table 7). Missing observations took the following form: 43 hot spots without corresponding hot spots in 31 patients and 3 nodes without corresponding hot spots.

Table 7. Location Agreement between Scintigraphic Imaging and Gamma Counter Findings

<table>
<thead>
<tr>
<th></th>
<th>Melanoma</th>
<th>Breast Cancer</th>
<th>Head and Neck Cancer</th>
<th>Overall Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement of Hot Spot and Hot Node Location *</td>
<td>182/206; 88% (83%, 93%)**</td>
<td>116/147; 79% (70%, 88%)**</td>
<td>95/115; 83% (76%, 90%)**</td>
<td>393/468; 84% (81%, 87%)**</td>
</tr>
</tbody>
</table>

* Denominator equals total number of hot spots and/or hot nodes. Numerator equals the numbers where hot spots and hot nodes agreed in location.

** 95% Confidence Intervals.

14.3 Lymphatic Mapping
In Studies 1 and 2 in melanoma and breast cancer, efficacy analyses were based upon comparisons of the number and proportion of resected lymph nodes that contained a lymph node tracer (Lymphoseek and/or blue dye) or neither tracer. Evaluable lymph nodes were resected from 176 Study 1 patients and 152 Study 2 patients who received Lymphoseek at the dose of 0.5 to 2 mCi in 50 mcg administered 15 minutes to 30 hours prior to surgery. Table 8 shows the distribution of resected lymph nodes by the presence or absence of a tracer. Most of the resected lymph nodes were identified by either Lymphoseek (LS) or blue dye (BD) or both. Significantly more resected lymph nodes were identified by Lymphoseek in comparison to blue dye.

Table 8. Resected Lymph Nodes and Content of Lymphoseek (LS) and/or Blue Dye (BD) from Studies in Breast Cancer and Melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor</th>
<th>Nodes</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BD Present</td>
<td>LS Present</td>
<td>Only BD Present</td>
<td>Only LS Present</td>
<td>Neither BD nor LS Present</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>Melanoma</td>
<td>187</td>
<td>65% (57%, 72%)</td>
<td>93% (88%, 96%)</td>
<td>2% (0.5%, 5%)</td>
<td>29% (23%, 37%)</td>
<td>6% (3%, 10%)</td>
</tr>
<tr>
<td></td>
<td>Breast Cancer</td>
<td>192</td>
<td>70% (63%, 77%)</td>
<td>89% (83%, 93%)</td>
<td>7% (4%, 12%)</td>
<td>26% (20%, 32%)</td>
<td>4% (2%, 8%)</td>
</tr>
<tr>
<td>Two</td>
<td>Melanoma</td>
<td>198</td>
<td>59% (51%, 66%)</td>
<td>99% (97%, 100%)</td>
<td>0 (0%, 2%)</td>
<td>41% (34%, 48%)</td>
<td>1% (0%, 3%)</td>
</tr>
<tr>
<td></td>
<td>Breast Cancer</td>
<td>181</td>
<td>62% (55%, 70%)</td>
<td>100% (98%, 100%)</td>
<td>0 (0%, 2%)</td>
<td>38% (30%, 45%)</td>
<td>1% (0%, 2%)</td>
</tr>
</tbody>
</table>

The percentages may not add to 100% due to rounding. 95% Confidence Intervals (CI) are based on Exact Binomial and represent the spread in the individual estimates.

In Studies 1 and 2 lymphatic mapping was performed in 328 patients with melanoma or breast cancer. The overall rate of lymph node detection by Lymphoseek at the patient level was 97% (319/328). The average number of lymph nodes detected by Lymphoseek was approximately 2 per patient.

14.4 Guiding Sentinel Lymph Node Biopsy
In Study 3 in patients with SCC of the oral cavity (n=79), skin (n=5), and lip (n=1), pathology findings for Lymphoseek-identified nodes (sentinel lymph nodes) were compared to the pathology findings of all other lymph nodes removed during the scheduled elective node dissection to determine the false negative rate of Lymphoseek. Thirty-nine patients were determined to have pathology-positive regional lymph nodes. In these patients, the Lymphoseek false negative rate for detecting patients with cancer-positive nodes was 2.6% (95% CI: 0.06% to 13.5%). In this study the pathology-positive nodes were all found in patients with SCC of the oral cavity.

Supportive analyses were conducted in Studies 1 and 2 in patients with breast cancer or melanoma. The presence or absence of Lymphoseek in nodes resected from patients determined by pathology staging to have lymphatic spread of cancer (n=64) was evaluated. The overall patient level rate for identifying at least one cancer-positive node in these pathology-positive patients (both cancers combined) was 97%. Lymphoseek identified 27 out of 29 node positive breast cancer patients and all of the 35 node positive melanoma patients.

16 HOW SUPPLIED/STORAGE AND HANDLING
The Kit for the preparation of Lymphoseek (technetium Tc 99m tilmanocept) injection (NDC 65857-425-05) includes:

- Five vials of Tilmanocept Powder, 250 mcg (NDC 65857-400-01)
- Prescribing information
- Five labels for shields
- Twenty-five labels for product vials and individual syringes

The Kit for the preparation of Lymphoseek (technetium Tc 99m tilmanocept) injection (NDC 65857-450-05) includes:

- Five vials of Tilmanocept Powder, 250 mcg (NDC 65857-400-01)
- Five vials of DILUENT for Lymphoseek (NDC 65857-401-45)
- Prescribing information
- Five labels for shields
- Twenty-five labels for product vials and individual syringes

Storage
Store Kit for the preparation of Lymphoseek (technetium Tc 99m tilmanocept) injection in the original packaging at USP controlled room temperature 20°C - 25°C (68°F - 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store radiolabeled Lymphoseek in radiation shielding at room temperature. Use radiolabeled Lymphoseek within 6 hours of preparation.

Handling
This Kit for the preparation of Lymphoseek (technetium Tc 99m tilmanocept) injection is approved for distribution to persons licensed by the U.S. Nuclear Regulatory Commission to use by product material identified in 10 CFR 35.200 or under an equivalent license issued by an Agreement State.

17 PATIENT COUNSELING INFORMATION
- Advise patients to seek medical attention for reactions following injection of Lymphoseek such as difficulty breathing, skin rash, or other allergy manifestations.
- Inform nursing women to pump and discard breast milk for at least 24 hours following administration of Lymphoseek injection [see Use in Specific Populations (8.2)]
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Ammonia N-13 Injection, USP safely and effectively. See full prescribing information for Ammonia N-13 Injection, USP.

Ammonia N-13 Injection, USP for intravenous use

Initial U.S. Approval: 2007

INDICATIONS AND USAGE

Ammonia N-13 Injection, USP is a radiopharmaceutical agent for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease (1).

Dosage and Administration

Rest Imaging Study (2.1):
- Aseptically withdraw Ammonia N-13 Injection, USP from its container and administer 10-20 mCi (0.368 – 0.736 GBq) as a bolus through a catheter inserted into a large peripheral vein.
- Start imaging 3 minutes after the injection and acquire images for a total of 10-20 minutes.

Stress Imaging Study (2.2):
- If a rest imaging study is performed, begin the stress imaging study 40 minutes or more after the first Ammonia N-13 Injection, USP to allow sufficient isotope decay.
- Administer a pharmacologic stress-inducing drug in accordance with its labeling.
- Aseptically withdraw Ammonia N-13 Injection, USP from its container and administer 10-20 mCi (0.368 – 0.736 GBq) of Ammonia N-13 Injection, USP as a bolus at 8 minutes after the administration of the pharmacologic stress-inducing drug.
- Start imaging 3 minutes after the Ammonia N-13 Injection, USP and acquire images for a total of 10-20 minutes.

Patient Preparation (2.3):
- To increase renal clearance of radioactivity and to minimize radiation dose to the bladder, hydrate the patient before the procedure and encourage voiding as soon as each image acquisition is completed and as often as possible thereafter for at least one hour.

FULL PRESCRIBING INFORMATION: CONTENTS*  

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Rest Imaging Study
2.2 Stress Imaging Study
2.3 Patient Preparation
2.4 Radiation Dosimetry
2.5 Drug Handling

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use

11 DESCRIPTION

11.1 Chemical Characteristics
11.2 Physical Characteristics

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
15 REFERENCES

17 PATIENT COUNSELING INFORMATION

17.1 Precautionary Hydration
17.2 Post-study Voiding
17.3 Post-study Breastfeeding Avoidance

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

Table 1: N-13 Absorbed Radiation Dose Per Unit Activity (rem/mCi) for Adults and Pediatric Groups

<table>
<thead>
<tr>
<th>Organs</th>
<th>Adult</th>
<th>15-year old</th>
<th>5-year old</th>
<th>1-year old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.0083</td>
<td>0.0006</td>
<td>0.0061</td>
<td>0.025</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>0.030</td>
<td>0.0037</td>
<td>0.0056</td>
<td>0.009</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.009</td>
<td>0.0011</td>
<td>0.0019</td>
<td>0.026</td>
</tr>
<tr>
<td>Brain</td>
<td>0.016</td>
<td>0.010</td>
<td>0.017</td>
<td>0.019</td>
</tr>
<tr>
<td>Breast</td>
<td>0.0067</td>
<td>0.0067</td>
<td>0.010</td>
<td>0.017</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.0065</td>
<td>0.0008</td>
<td>0.0015</td>
<td>0.004</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.0067</td>
<td>0.0081</td>
<td>0.0013</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Table 1: N-13 Absorbed Radiation Dose Per Unit Activity (rem/mCi) for Adults and Pediatric Groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Adult</th>
<th>15-year old</th>
<th>5-year old</th>
<th>1-year old</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong></td>
<td>0.0493</td>
<td>0.011</td>
<td>0.010</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Lungs</strong></td>
<td>0.0059</td>
<td>0.011</td>
<td>0.019</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Kidneys</strong></td>
<td>0.0061</td>
<td>0.0085</td>
<td>0.014</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>0.0063</td>
<td>0.0078</td>
<td>0.012</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Spleen</strong></td>
<td>0.0067</td>
<td>0.013</td>
<td>0.009</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Aorta</strong></td>
<td>0.0063</td>
<td>0.0088</td>
<td>0.013</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Other tissues</strong></td>
<td>0.0059</td>
<td>0.0070</td>
<td>0.012</td>
<td>0.018</td>
</tr>
</tbody>
</table>

-----Dosage and Strengths-----
Glass vial containing 0.138-1.387 GBq (3.75-37.5 mCi/mL) of Ammonia N-13 Injection, USP in aqueous 0.9 % sodium chloride solution (approximately 8 mL to 10 mL volume) is suitable for intravenous administration.

-----Contraindications-----
None

-----Warnings and Precautions-----
Ammonia N-13 Injection, USP may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker (5).

-----Adverse Reactions-----
No adverse reactions have been reported for Ammonia N-13 Injection, USP based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting system (6).

To report SUSPECTED ADVERSE REACTIONS, contact Cardinal Health at 1-800-618-2768 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-----Use in Specific Populations-----

1. It is not known whether this drug is excreted in human milk. Alternatives to breastfeeding (e.g. using stored breast milk or infant formula) should be used for 2 hours (>10 half-lives of radioactive decay for N-13 isotope) after administration of Ammonia N-13 Injection, USP (8.3).

2. The safety and effectiveness of Ammonia N-13 Injection, USP has been established in pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2015

5.00013
0.0067
0.0063
0.0061
0.017
0.012
0.013
0.019
0.017
0.010
0.0081
0.0013
0.041
0.0041
0.0035
0.0023
0.0019
0.0017
0.0010
0.0008
0.00013
0.0041
0.0089
0.012
0.014
0.019
0.026
0.021
0.035
0.039
0.041
0.023
Ammonia N-13 Injection, USP is a radiolabeled analog of ammonia that is distributed to all organs of the body after intravenous administration. It is extracted from the blood into the myocardial cells where it is metabolized to glutamine N-13 and retained in the cells. The presence of ammonia N-13 and glutamine N-13 in the myocardium allows for PET imaging of the myocardium.

Ammonia N-13 Injection, USP is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient, [13N] ammonia, has the radioactive decay for N-13 isotope (after administration of the drug or avoid use of the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Ammonia N-13 Injection, USP has been established in pediatric patients based on available data in adults [see Dosage and Administration (2.4)].

11 DESCRIPTION

11.1 Chemical Characteristics

Ammonia N-13 Injection, USP is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient, [13N] ammonia, has the molecular formula of [13N]NH3, with a molecular weight of 16.02, and has the following chemical structure:

\[
\begin{align*}
N \quad H \\
\quad H
\end{align*}
\]

Ammonia N-13 Injection, USP is provided as a ready to use sterile, pyrogen-free, clear and colorless solution. Each mL of the solution contains 0.338 GBq (10.5 mCi) of [13N] ammonia at the end of synthesis (EOS) reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 to 7.5. The recommended dose of radioactivity (10-20 mCi) is associated with a theoretical mass dose of 0.5-1.0 picomoles of ammonia.

12.2 Pharmacokinetics

Following intravenous injection, ammonia N-13 enters the myocardium through the coronary arteries. The PET technique measures myocardial blood flow based on the assumption of a three-compartmental disposition of intravenous ammonia N-13 in the myocardium. In this model, the value of the rate constant, which represents the delivery of blood to myocardium, and the fraction of ammonia N-13 extracted into the myocardial cells, is a measure of myocardial blood flow. Optimal PET imaging of the myocardium is generally achieved between 10 to 20 minutes after administration.

Fifty-six percent of the introduced radioactivity is excreted in the urine and approximately 19% is expired in the expired. The mass dose of Ammonia N-13 Injection, USP is very small as compared to the normal range of ammonia in the blood (0.72-3.30 mg) in a healthy adult man [see Description (11.3)].

The pharmacokinetics of Ammonia N-13 Injection, USP have not been studied in early irritable, hipopically impaired, or pediatric patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Ammonia N-13 Injection, USP. Genotoxicity assays and impairment of male and female fertility studies with Ammonia N-13 Injection, USP have not been performed.

14 CLINICAL STUDIES

In a descriptive, prospective, blinded image interpretation study of adult patients with known or suspected coronary artery disease, myocardial perfusion defects in stress and rest PET images obtained with Ammonia N-13 (N=111) or Rubidium 82 (N=82) were compared to changes in stress flow reserve (SFR) as determined by coronary angiography. The principal outcome of the study was the evaluation of PET defect severity relative to SFR.

PET perfusion defects at rest and stress for seven cardiac regions (anterior, apical, anteroseptal, posteroseptal, anterolateral, posterolateral, and inferior walls) were graded on a 0 to 5 scale defined as normal (0), possible (1), probable (2), mild (3), moderate (4), and severe (5) defects. Coronary angiograms were used to measure absolute and relative stenosis dimensions and to calculate stenosis flow reserve defined as the maximum value of flow at maximum coronary vasodilatation relative to rest flow under standardized hemodynamic conditions. SFR scores ranged from 0 (total occlusion) to 5 (normal).

With increasing impairment of flow reserve, the subjective PET defect severity increased. A PET defect score of 2 or higher was positively correlated with flow reserve impairment (SFR<3).

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

Ammonia N-13 Injection, USP is packaged in 10 mL multiple dose glass vial containing between 1.11–11.1 GBq (30-300 mCi) of [13N] ammonia, at the end of synthesis (EOS) reference time, in 0.9% sodium chloride injection solution in approximately 8 mL to 10 mL volume. The recommended dose of radioactivity (10-20 mCi) is associated with a theoretical mass dose of 0.5-1.0 picomoles of Ammonia.

NDC 68587-200-10

Storage
Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Use the solution within 60 minutes of the End of Synthesis (EOS) calibration.

17 PATIENT COUNSELING INFORMATION

17.1 Pre-study Hydration

Instruct patients to drink plenty of water or other fluids (as indicated) in the 4 hours before their PET study.

17.2 Post-study Voidsing

Instruct patients to void after completion of each image acquisition session and as often as possible for one hour after the PET scan ends.

17.3 Post-study Breastfeeding Avoidance

Instruct nursing patients to substitute stored breast milk or infant formula for breast milk for 2 hours after administration of Ammonia N-13 Injection, USP.

Manufactured by: Cardinal Health 414, LLC
7000 Cardinal Place
Dublin, OH 43017

Distributed by: Cardinal Health 414, LLC
7000 Cardinal Place
Dublin, OH 43017

Revised: 06/2013
NPS-P-0001 ver 2.0

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ammonia N-13 Injection, USP is a radiolabeled analog of ammonia that is distributed to all organs of the body after intravenous administration. It is extracted from the blood into the myocardial cells where it is metabolized to glutamine N-13 and retained in the cells. The presence of ammonia N-13 and glutamine N-13 in the myocardium allows for PET imaging of the myocardium.

Table 1: Principal Radiation Emission Data for Nitrogen 13

<table>
<thead>
<tr>
<th>Radiation/Emission</th>
<th>% Per Disintegration</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position(°)</td>
<td>%</td>
<td>GBq (mCi)</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>1590 (55)</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>200  (6)</td>
</tr>
</tbody>
</table>
| a) Produced by position annihilation. The specific gamma ray constant (point source air kerma coefficient) for nitrogen-13 is 5.9 R/hr/mC (1.39 x 10^7 Gy/h/keV/cm). The half-value layer (HVL) of lead (Pb) for 511 keV photons is 4 mm, or 2.9 mm tungsten (W) alloy. Selected coefficients of attenuation are listed in Table 3 as a function of lead thickness.

Table 3: Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

<table>
<thead>
<tr>
<th>Shield Thickness (Pb) mm</th>
<th>Shield Thickness (W) Alloys mm</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.25</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>0.01</td>
</tr>
<tr>
<td>4</td>
<td>1.00</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The table lists fractions remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 4: Physical Decay Chart for Nitrogen 13

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>5</td>
<td>0.906</td>
</tr>
<tr>
<td>10</td>
<td>0.499</td>
</tr>
<tr>
<td>15</td>
<td>0.292</td>
</tr>
<tr>
<td>30</td>
<td>0.124</td>
</tr>
<tr>
<td>60</td>
<td>0.016</td>
</tr>
</tbody>
</table>

a) calibration time
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Sodium Fluoride F-18 Injection, USP, safely and effectively. See full prescribing information for Sodium Fluoride F-18 Injection, USP.

Sodium Fluoride F-18 Injection, USP
For Intravenous Use
Initial U.S. Approval: 2011

--INDICATIONS AND USAGE--
Sodium Fluoride F-18 Injection, USP, is a radiopharmaceutical (PET) imaging agent for the detection of abnormal osteogenic activity.

--DOSE AND ADMINISTRATION--

- Administer 300-450 MBq (8-12 mCi) as an intravenous injection.

--CONTRAINDICATIONS--

- Allergic Reactions: As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.

--WARNINGS AND PRECAUTIONS--

- Cancer Risk: Sodium Fluoride F-18 Injection, USP, may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker.

--ADVERSE REACTIONS--

No adverse reactions have been reported for Sodium Fluoride F-18 Injection, USP, based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems.

Full prescribing information: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Radiation Safety - Drug Handling
2.2 Radiation Safety - Patient Preparation
2.3 Drug Preparation and Administration
2.4 Recommended Dose for Adults
2.5 Recommended Dose for Pediatric Patients
2.6 Radiation Dosimetry
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Allergic Reactions
5.2 Radiation Risks
6 ADVERSE REACTIONS
7 USE IN SPECIFIC POPULATIONS
8 Pregnancy
8.3 Nursing Mothers
International Commission on Radiological Protection for Sodium Fluoride Injection [2]. The bone, bone marrow and urinary bladder are considered target and critical organs.

Table 1. Estimated Absorbed Doses after Intravenous Administration of Sodium Fluoride F-18 Injection, USP

<table>
<thead>
<tr>
<th>Organ</th>
<th>Organ</th>
<th>Organ</th>
<th>Organ</th>
<th>Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
<td>15 year</td>
<td>5 year</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td>70 kg†</td>
<td>56.8 kg†</td>
<td>33.2 kg†</td>
<td>19.8 kg†</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.0062</td>
<td>0.012</td>
<td>0.018</td>
<td>0.028</td>
</tr>
<tr>
<td>Brain</td>
<td>0.0066</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.060</td>
<td>0.050</td>
<td>0.079</td>
<td>0.13</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.0028</td>
<td>0.0061</td>
<td>0.0097</td>
<td>0.015</td>
</tr>
<tr>
<td>Gl</td>
<td>0.0044</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Gallbladder wall</td>
<td>0.0068</td>
<td>0.008</td>
<td>0.013</td>
<td>0.019</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.0066</td>
<td>0.012</td>
<td>0.018</td>
<td>0.028</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.0058</td>
<td>0.010</td>
<td>0.016</td>
<td>0.026</td>
</tr>
<tr>
<td>Upper large intestine wall</td>
<td>0.0058</td>
<td>0.010</td>
<td>0.016</td>
<td>0.026</td>
</tr>
<tr>
<td>Lower large intestine wall</td>
<td>0.012</td>
<td>0.016</td>
<td>0.025</td>
<td>0.037</td>
</tr>
<tr>
<td>Heart wall</td>
<td>0.0039</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.019</td>
<td>0.025</td>
<td>0.036</td>
<td>0.053</td>
</tr>
<tr>
<td>Liver</td>
<td>0.0040</td>
<td>0.0084</td>
<td>0.013</td>
<td>0.021</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.0041</td>
<td>0.0084</td>
<td>0.013</td>
<td>0.020</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.0060</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.011</td>
<td>0.016</td>
<td>0.023</td>
<td>0.036</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.0048</td>
<td>0.0096</td>
<td>0.015</td>
<td>0.023</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.028</td>
<td>0.053</td>
<td>0.088</td>
<td>0.18</td>
</tr>
<tr>
<td>Skin</td>
<td>0.0040</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.0042</td>
<td>0.0088</td>
<td>0.014</td>
<td>0.021</td>
</tr>
<tr>
<td>Testes</td>
<td>0.0078</td>
<td>0.013</td>
<td>0.021</td>
<td>0.033</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.0035</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.0044</td>
<td>0.0084</td>
<td>0.013</td>
<td>0.020</td>
</tr>
<tr>
<td>Urinary bladder wall</td>
<td>0.25</td>
<td>0.27</td>
<td>0.4</td>
<td>0.61</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.039</td>
<td>0.023</td>
<td>0.037</td>
<td>0.057</td>
</tr>
<tr>
<td>Other tissue</td>
<td>N/A</td>
<td>0.010</td>
<td>0.015</td>
<td>0.024</td>
</tr>
<tr>
<td>Effective</td>
<td>0.027</td>
<td>0.034</td>
<td>0.052</td>
<td>0.086</td>
</tr>
</tbody>
</table>

* Data from ICRP publication 53, Radiation Dose to Patients from Radiopharmaceuticals, Ann ICRP, Volume 18, pages 15 and 74, 1987.
2.7 Imaging Guidelines
- Imaging of Sodium Fluoride F-18 Injection, USP, can begin 1–2 hours after administration; optimally at 1 hour post administration.
- Encourage the patient to void immediately prior to imaging the fluoride F-18 radioactivity in the lumbar spine or bony pelvis.

3 DOSAGE FORMS AND STRENGTHS
Multiple-dose vial containing 370–7,400 MBq/mL (10–200 mCi/mL) at EOS reference time of no-carrier-added sodium fluoride F-18, in aqueous 0.9% sodium chloride solution. Sodium Fluoride F-18 Injection, USP, is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Allergies
As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.

5.2 Radiation Risks
Sodium Fluoride F-18 Injection, USP, may increase the risk of cancer. Carcinogenic and mutagenic studies with Sodium Fluoride F-18 Injection, USP, have not been performed. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration (2.1)].

6 ADVERSE REACTIONS
No adverse reactions have been reported for Sodium Fluoride F-18 Injection, USP, based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known.

7 DRUG INTERACTIONS
The possibility of interactions of Sodium Fluoride F-18 Injection, USP, with other drugs taken by patients undergoing PET imaging has not been studied.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C.

8.2 Breastfeeding
It is not known whether Sodium Fluoride F-18 Injection, USP, is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to interrupt nursing after administration of Sodium Fluoride F-18 Injection, USP, or to administer Sodium Fluoride F-18 Injection, USP, taking into account the importance of the drug to the mother.

8.3 Pediatric Use
It is not known whether Sodium Fluoride F-18 Injection, USP, is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to interrupt nursing after administration of Sodium Fluoride F-18 Injection, USP, or to administer Sodium Fluoride F-18 Injection, USP, taking into account the importance of the drug to the mother.

11 DESCRIPTION
11.1 Chemical Characteristics
Sodium Fluoride F-18 Injection, USP, is a positron emitting radiopharmaceutical, containing no-carrier-added, radioactive fluoride F-18 that is used for diagnostic purposes in conjunction with PET imaging. It is administered by intravenous injection. The active ingredient, sodium fluoride F-18, has the molecular formula Na18F with a molecular weight of 40.99, and has the following chemical structure:

11.2 Physical Characteristics
Fluoride F-18 decays by positron (β+) emission and has a half-life of 109.7 minutes. Ninety-seven percent of the decay results in emission of a positron with a maximum energy of 0.63 keV and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the decay of the radionuclide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Fluoride F-18 ion normally accumulates in the skeleton in an even fashion, with greater deposition in the antebraconial skeleton (vertebra and pelvis) than in the appendicular skeleton and greater deposition in the bones around joints than in the shafts of long bones.

12.2 Pharmacodynamics
Increased fluoride F-18 ion deposition in bone can occur in areas of increased osteogenic activity during growth, infection, malignancy (primary or metastatic) following trauma, or inflammation of bone.

12.3 Pharmacokinetics
After intravenous administration, fluoride F-18 ion is rapidly cleared from the plasma in a bieponential manner. The first phase has a half-life of 0.4 h, and the second phase has a half-life of 2.6 h. Essentially all the fluoride F-18 that is delivered to bone by the blood is retained in the bone. One hour after administration of fluoride, F-18 only about 10% of the injected dose remains in the blood. Fluoride F-18 diffuses through capillaries into bone extracellular fluid space, where it becomes bound by chemisorption at the surface of bone crystals, preferentially at sites of newly mineralizing bone.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to assess reproductive toxicity, mutagenesis and carcinogenesis potential of Sodium Fluoride F-18 Injection, USP, have not been performed.

14 CLINICAL STUDIES
14.1 Metastatic Bone Disease
The doses used in reported studies ranged from 2.7 mCi to 20 mCi (100 MBq to 740 MBq), with an average median dose of 10 mCi (370 MBq) and an average mean dose of 9.2 mCi (340 MBq). In PET imaging of bone metastases with Sodium Fluoride F-18 Injection, USP, locally increased tracer uptake is seen in both osteolytic and osteoblastic bone lesions. Negative PET imaging results with Sodium Fluoride F-18 Injection, USP, do not preclude the diagnosis of bone metastases. Also, as bone benign lesions are also detected by Sodium Fluoride F-18 Injection, USP, positive PET imaging results cannot replace biopsy to confirm a diagnosis of cancer.

14.2 Other Bone Disorders
The doses used in reported studies ranged from 2.43 mCi to 15 mCi (90 MBq to 555 MBq), with an average median dose of 8.0 mCi (300 MBq) and an average mean dose of 7.6 mCi (280 MBq).


16 HOW SUPPLIED/STORAGE AND HANDLING
Sodium Fluoride F-18 Injection, USP, is supplied in a multiple-dose Type I glass vial with elastomeric stopper and aluminum crimp seal containing between 370 and 7,400 MBq (10–200 mCi) of no-carrier-added sodium fluoride F-18, at the EOS reference time, in aqueous 0.9% sodium chloride solution. The total volume and total radioactivity per vial are variable. Each vial is enclosed in a shielded container of appropriate thickness.

17 PATIENT COUNSELING INFORMATION
17.1 Pre-Study Hydration
Encourage patients to drink at least 500 mL of water prior to drug administration.

17.2 Post-Study Voiding
To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible, use a toilet and flush several times after each use; wash hands thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, wash the clothing separately.

17.3 Radiation Safety
Radiation safety is the responsibility of the radiation safety officer. Protective clothing and equipment may be worn by patients, staff, and visitors present during imaging and handling.

17.4 Disposal
Waste from (>5 mCi; >185 MBq) Sodium Fluoride F-18 Injection, USP, should be disposed of as a radioactive waste.

17.5 Mass Radiopharmaceuticals
Mass radiopharmaceuticals are defined as any radiopharmaceutical that contains an activity greater than or equal to 50 GBq (1,300 MBq).

17.6 Nonmass Radiopharmaceuticals
Nonmass radiopharmaceuticals are defined as any radiopharmaceutical that contains an activity less than 50 GBq (1,300 MBq).

17.7 Waste Disposal Compliance
Manufactured by:
Cardinal Health 414, LLC
7000 Cardinal Place
Dublin, OH 43017

Distributed by:
Cardinal Health 414, LLC
7000 Cardinal Place
Dublin, OH 43017

NPI-00002 ver 1.0

Table 3 lists the fraction of radioactivity remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 4. Physical Decay Chart for Fluoride F-18

<table>
<thead>
<tr>
<th>Time Since Calibration</th>
<th>Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>1.00</td>
</tr>
<tr>
<td>15 minutes</td>
<td>0.90</td>
</tr>
<tr>
<td>30 minutes</td>
<td>0.826</td>
</tr>
<tr>
<td>60 minutes</td>
<td>0.683</td>
</tr>
<tr>
<td>90 minutes</td>
<td>0.500</td>
</tr>
<tr>
<td>220 minutes</td>
<td>0.250</td>
</tr>
<tr>
<td>440 minutes</td>
<td>0.060</td>
</tr>
<tr>
<td>12 hours</td>
<td>0.011</td>
</tr>
<tr>
<td>24 hours</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* calibration time

Table 5 lists the fraction of radioactivity remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.