For intravenous use only

**DESCRIPTION**

Ceretec is supplied as five packs of three vials for use in the preparation of technetium Tc99m exametazime, an intravenous imaging agent. Each vial contains 0.5 mCi (500 μCi) of technetium Tc99m, which is used to label leukocytes for diagnostic imaging. The solution is sterile and non-pyrogenic.

**ADDITIONAL INFORMATION**

- **Pharmacokinetics:**
  - The lipophilic Tc99m exametazime complex is rapidly cleared from the blood after intravenous injection. Uptake in the brain reaches a maximum of 3.5-7.0% of the injected dose.
  - Activity is seen in the gastrointestinal tract immediately after injection and about 50% of this is excreted through the kidneys and urine over the 48 hours after injection.

- **Radiopharmacokinetics:**
  - When technetium Tc99m pertechnetate is added to exametazime in the presence of stannous and stannic tin, a Tc99m complex of exametazime is formed. This complex is used to label leukocytes for diagnostic imaging.

- **Clinical Trials:**
  - Two clinical trials were performed with a total of 88 patients who had suspected intra-abdominal infection or inflammation. Subjects received both Tc99m labeled leukocytes and In111-labeled leukocytes. Images were obtained at 2 and 30 hours.

<table>
<thead>
<tr>
<th>Shield Thickness (Pb) mm</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>0.95</td>
<td>10^3</td>
</tr>
<tr>
<td>1.8</td>
<td>10^2</td>
</tr>
<tr>
<td>2.7</td>
<td>10^3</td>
</tr>
<tr>
<td>3.6</td>
<td>10^4</td>
</tr>
<tr>
<td>4.5</td>
<td>10^5</td>
</tr>
</tbody>
</table>

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals relative to the time of calibration are shown in Table 3.

<table>
<thead>
<tr>
<th>Hours Remaining</th>
<th>Fraction Remaining</th>
<th>Hours Remaining</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>0.399</td>
</tr>
<tr>
<td>2</td>
<td>0.795</td>
<td>9</td>
<td>0.355</td>
</tr>
<tr>
<td>3</td>
<td>0.708</td>
<td>10</td>
<td>0.317</td>
</tr>
<tr>
<td>4</td>
<td>0.651</td>
<td>11</td>
<td>0.282</td>
</tr>
<tr>
<td>5</td>
<td>0.563</td>
<td>12</td>
<td>0.252</td>
</tr>
<tr>
<td>6</td>
<td>0.502</td>
<td>24</td>
<td>0.063</td>
</tr>
</tbody>
</table>

*Calibration time (time of preparation)

**CLINICAL PHARMACOLOGY**

**General**

When technetium Tc99m pertechnetate is added to exametazime in the presence of stannous, a lipophilic technetium Tc99m complex is formed. This lipophilic complex is active in the body. It converts at approximately 12%/hour to less lipophilic species. When the secondary complex is separated from the lipophilic species, it is used to label the leukocytes. The useful life of the reconstituted agent is limited to 30 minutes. The in vitro addition of methylene blue to the Tc99m-exametazime will stabilize the complex for 4-6 hours. Methylene blue may be added to Tc99m for cerebral imaging. Methylene blue should not be used in the preparation of Tc99m-exametazime labeled leukocytes.

**Pharmacokinetics**

- Studies in normal volunteers have shown that the technetium Tc99m complex of the RRSSdilastosteroid of exametazime is rapidly cleared from the blood after intravenous injection. The uptake in the brain reaches a maximum of 3.5-7.0% of the injected dose within one minute of injection. Up to 15% of the activity is eliminated from the brain by 2 minutes post injection, after which little activity is lost for the following 24 hours except by physical decay of technetium Tc99m.

**In vivo recovery and very low lung and liver activity:** Label elution rate is up to 10% in the first hour.

**Pharmacodynamics**

- Tc99m-labeled leukocyte: Based upon in vivo recovery and very low lung and liver uptake, the labeled leukocytes are still functional. Following rejection of the Tc99m labeled leukocytes, the circulating granulocyte activity as a percentage of labeled granulocyte activity at 40 minutes after injection gave a mean of 37% (range 10-47%).

- During the first hour following injection of Tc99m labeled leukocytes, activity is seen in the lungs, liver, spleen, blood pool, bone marrow and the bladder. The kidneys (parenchyma and/or renal pelvis) and gall bladder may also be visualized. Over the first 1-6 hours, the Tc99m is visualized in the bowel. At 24 hours post-injection substantial colonic activity is seen. The normal areas visualized in earlier scans are still visible.

**CLINICAL TRIALS**

Two clinical trials were performed with a total of 88 patients who had suspected intra-abdominal infection or inflammation. Subjects received both Tc99m labeled leukocytes and In111-labeled leukocytes. Images were obtained at 2 and 30 hours.
minutes and at 2 and 4 hours and 24 hours. In two other clinical trials, in a total of 127 patients with suspected abdominal inflammation or infection received Tc99m labeled leukocytes. Imaging was at 24 hours in one study and at 1, 3 and 24 hours in the other. In all four studies images were blindly evaluated and the findings were confirmed by surgery, biopsy or other clinical data.

Based on the above 4 studies, between 2 to 4 hours Tc99m labeled leukocytes had 95-100% sensitivity and 62-85% specificity with similar numbers of false positive and false negative findings. The value of the 24 hour Tc99m labeled leukocyte images is inconsistent. In all studies the false positive and false negatives relate to the bowel background, the location of the site of infection/inflammation and whether or not it is contiguous with the bowel. The 24 hour films should be interpreted with great caution because of a high bowel background; false negatives were noted in both Tc99m and In111 labeled leukocytes.

Other studies suggest that the interpretation of the images could be affected by the presence of tumors, infarction and peritonitis, etc. Liver abscess may be missed because of the bowel background. Caution should be exercised in making the final diagnosis.

INDICATIONS AND USAGE

Technetium Tc99m exametazime scintigraphy (with or without methylene blue stabilization) may be useful as an adjunct in the detection of altered regional cerebral perfusion in stroke.

Tc99m exametazime without methylene blue stabilization is indicated for leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease.

CONTRAINDICATIONS

None known.

PRECAUTIONS

As with any injected product, acute hypersensitivity or allergic reactions are possible. Limited reports have been received of hypersensitivity reactions following administration of Tc99m labeled leukocytes prepared using Tc99m exametazime. However, the materials used in leukocyte cell separation may cause hypersensitivity reactions. It is essential that cells are washed free of sedimentation agents before they are reinjected into the patient.

In case of side effects following administration of radio-pharmaceuticals, users should ensure the availability of appropriate medical treatment at the time of administration of any radiopharmaceutical to the patient.

A thorough knowledge of the normal distribution of intravenously administered technetium Tc99m exametazime injection is essential in order to interpret pathologic studies accurately. Caution should be exercised in making the final diagnosis. Results can be affected by the presence of tumor, infarction, peritonitis, non-gastrointestinal or bony sites of inflammatory cell collections.

The contents of the Ceretec vial are not radioactive. After the sodium pertechnetate Tc99m is added, the product is radioactive and adequate shielding of the final preparation must be maintained. The contents of the Ceretec vial are intended only for use in preparation of technetium Tc99m exametazime injection and are NOT to be administered directly to the patient.

General

The contents of the Ceretec vial are sterile and pyrogen free. The vial contains no bacteriostatic preservative. It is essential that the user follow the directions carefully and adhere to strict aseptic procedures during preparation of the radiopharmaceutical.

Radiopharmaceuticals should be used only by or under the control of 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 governmental agency authorized to license the use of radionuclides.

To minimize radiation dose to the bladder, the patient should be encouraged to void when the examination is completed and as often thereafter as possible. Adequate hydration should be encouraged to permit frequent voiding.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies have not been performed to evaluate carcinogenic potential or whether exametazime affects fertility in males or females. When evaluated in the Ames test, exametazime increased the apparent rate of gene mutation in the TA100 strain of S. typhimurium. Exametazime did not cause chromosomal aberrations in vitro (Chinese Hamster Ovary cells) or in vivo (rat bone marrow).

Pregnancy Category C

Animal reproduction studies have not been conducted with Tc99m exametazime. It is also not known whether Tc99m exametazime can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity. Therefore, Tc99m exametazime should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.
1) Prepare a 60 mL syringe containing 10 mL acid citrated extrose solution.

2) Using aseptic venipuncture technique and the prepared syringe (from Step 1) withdraw 0.5 mL Methylene Blue Injection USP 1% into a sterile syringe and inject into a 10 mL syringe containing 5 mL of sterile eluate from a technetium Tc99m generator.

3) Add methylene blue stabilizing solution from Step 1 to the reconstituted vial, swirling gently to mix.

4) Determine the radiochemical purity of the solution (see Radiochemical Purity Measurement section). A radiochemical purity greater than 80% is necessary for product acceptance.

5) Maintain adequate shielding of the radioactive preparation.

6) The injection may be used for up to 4 hours in cerebrovascular studies.

7) Prior to patient injection, attach enclosed syringe filter.

8) The pH of the prepared injection is 6.5-7.5.

9) Also see section on Cautionary Notes for all Preparations.

Procedure for the Preparation of Technetium Tc99m Exametazime Injection Without Methylene Blue Stabilizer

Note: Sterile technique must be used throughout. The user should wear waterproof gloves during the handling and administration procedure.

1) Place one of the vials in a suitable shielding container and sanitize the rubber septum with an isopropyl alcohol swab.

2) Using a 10 mL syringe, inject into the shielded vial 5 mL of sterile eluate from a technetium Tc99m generator (see notes 1-3). Before withdrawing the syringe from the vial, withdraw 5 mL of gas from the space above the solution to normalize the pressure in the vial. Gently invert the shielded vial for 10 seconds to ensure complete dissolution of the powder.

3) Assay the total activity and calculate the volume to be injected. The patient dose should be measured in a suitable radioactivity calibration system immediately prior to administration.

4) Complete the label provided and attach to the vial shield. The technetium Tc99m exametazime injection is ready for quality control.

5) Maintain adequate shielding of the radioactive preparation.

6) Do not use the preparation more than 30 minutes after time of formulation. Discard any unused material.

7) Visually inspect the reconstituted material at a safe distance behind lead glass, and do not use if there is evidence of foreign matter.

8) The injection may be prepared for use in cerebral scintigraphy or for use in the preparation of Tc99m labeled WBCs.

9) The pH of the prepared injection is 9.0-9.8.

10) Also see section on Cautionary Notes for all Preparations.

Procedure for Radiolabeling of Autologous Leukocytes with Technetium Tc99m Exametazime Injection

1) Quality control kit which includes all necessary components (available from Biodex Medical Systems Inc/ Phone # 516-924-9000 - Cat. #151-660).
2) Individual supplies:
SA ITLC strips 20 cm x 2.0 cm
Whatman No. 1 strips 6 cm x 0.7 cm
MEK (methyl ethyl ketone (butanone)) (Aldrich Cat. #27069-5, 99.9 % HPLC Grade)
0.9% aqueous sodium chloride (non-bacteriostatic)
50% aqueous acetonitrile (Aldrich Cat. #27071-7, 99.9 % HPLC Grade)
Dilute with non-bacteriostatic Water for injection
Glass test tubes (12 x 75 mm)
Glass measuring cylinders (100 mL) with covers
1 mL syringes with 25 gauge needles
3) Suitable counting equipment.
Method
1) Prepare 1 chromatography tube containing 0.2-0.3 mL of 50% acetonitrile. Prepare 2 100 mL cylinders each containing a 1 cm depth of fresh MEK and 0.9% sodium chloride, respectively. Identify the solvent in each cylinder.
2) Prepare 2 SA ITLC strips and 1 Whatman No. 1 paper strip. Mark the Whatman strip 1.0 cm from the bottom as the point of origin. Mark the SA ITLC strips 2.5 cm from the bottom as the point of origin. Mark both the SA ITLC strips at 14 cm above the origin (solvent front).
3) Reconstitute a Ceretec vial according to this insert.
4) Apply at least 5 µL samples of Ceretecto the origin of the 3 strips within 15 minutes of reconstitution. Immediately place 1 SA ITLC strip into the MEK tank, the second SA ITLC strip into the saline tank and the Whatman No. 1 paper strip into the 50% acetonitrile tube. Make sure strips are not adhering to the side of the test tube.
5) The SA ITLC MEK strip takes approximately 15 minutes to run. When the eluate has reached the solvent front remove the strip from the tube with forceps and immediately cut 1.0 cm above the origin.
6) The SA ITLC saline strip takes approximately 15 minutes to run. When the eluate has reached the solvent front remove the strip from the tube with forceps and immediately cut 2.5 cm above the origin.
7) The Whatman No. 1 paper CH3 CN strip takes approximately 100 seconds to run. When the eluate has reached the solvent front mark remove the strip from the tube with forceps and immediately cut 1.0 cm above the origin.
8) Count the separate sections of each strip to determine the activity distribution. Make sure proper counting geometry is maintained attempting to reduce any interference from equipment dead time.
9) Determine:
% bottom of saline strip – % bottom of MEK strip
(= % lipophilic exametazime complex)
% top of saline strip (= % pertechnetate)
% bottom of Whatman No. 1 paper strip (= % reduced-hydrolyzed-Tc)
A radiochemical purity of >80% may be expected provided the measurement has been carried out within 4 hours of reconstitution for stabilized Ceretec and 30 minutes for Ceretec used for WBC labeling.
Interpretation of Chromatogram
System 1 (SA ITLC: MEK (butanone))
Secondary Tc exametazime complex and reduced-hydrolyzed-Tc remain at the origin.
Lipophilic Tc exametazime complex and pertechnetate migrate at Rf 0.8-1.0.
System 2 (SA ITLC: 0.9% sodium chloride)
Lipophilic-Tc exametazime complex, secondary Tc exametazime complex and reduced-hydrolyzed-Tc remain at the origin. Pertechnetate migrates at Rf 0.8-1.0.
System 3 (Whatman No. 1: 50% aqueous acetonitrile)
Reduced-hydrolyzed-Tc remains at the origin. Lipophilic Tc exametazime complex, secondary Tc exametazime complex and pertechnetate migrate at Rf 0.8-1.0.
RADIATION DOSIMETRY
Based on human data, the absorbed radiation doses to an average human adult (70 kg) from an intravenous injection of this product are estimated below. The values are listed as µGy/MBq, rads/mCi with urination every 2 hours. Bladder wall dose is 19 µGy/MBq, 0.07 rads/mCi with 4 hour urination and 89 µGy/MBq, 0.33 rads/mCi with no urination.

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Absorbed radiation dose Tc99m exametazime injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µGy/MBq rads/mCi</td>
</tr>
<tr>
<td></td>
<td>mGy/740 MBq rads/20 mCi</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>51.0 0.19</td>
</tr>
<tr>
<td>Kidney</td>
<td>25.90 2.60</td>
</tr>
<tr>
<td>Thyroid</td>
<td>19.98 2.00</td>
</tr>
<tr>
<td>Upper Large</td>
<td>15.54 1.58</td>
</tr>
<tr>
<td>Intestine Wall</td>
<td>11.10 1.08</td>
</tr>
<tr>
<td>Lower Large</td>
<td>11.04 1.08</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>9.62 0.94</td>
</tr>
<tr>
<td>Brain</td>
<td>5.11 0.52</td>
</tr>
<tr>
<td>Ovaries</td>
<td>4.66 0.46</td>
</tr>
<tr>
<td>Testes</td>
<td>2.66 0.26</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>2.52 0.26</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>3.55 0.36</td>
</tr>
<tr>
<td>Eyes</td>
<td>5.11 0.52</td>
</tr>
</tbody>
</table>

* Data supplied by Oak Ridge Associated Universities, Radiopharmaceutical Internal Dose Information Center.

Table 5. In vivo Localization of Tc99m Labeled Leukocytes
The estimated absorbed radiation doses to various organs following the intravenous administration of Tc99m labeled leukocytes given by ICRP 53** are as follows (bladder voiding every 3.5 hours)

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Absorbed Radiation Dose (mGy per 200 MBq)</th>
<th>rads/25 mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>13.89</td>
<td></td>
</tr>
<tr>
<td>Red Marrow</td>
<td>2.04</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>1.85</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Testes</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td>0.35</td>
<td></td>
</tr>
</tbody>
</table>

Effective Dose Equivalent (EDE) 3.6 mSv/200 MBq.

HOW SUPPLIED
The kit comprises five individual vials of sterile, non-pyrogenic, freeze-dried mixture of exametazime, stannous chloride dihydrate and sodium chloride, ten radiation labels, five radiochemical purity worksheets, five labeling efficiency worksheets, one package insert, five individual vials of Methylene Blue Injection USP 1%, five individual vials of 0.003 M Monobasic Sodium Phosphate USP and Dibasic Sodium Phosphate USP in 0.9% Sodium Chloride Injection USP and fifteen 0.45 µm syringe filters.

NDC 17156-023-05

Storage
Store the kit at 15°-25°C (59°-77°F).
Store the formulated drug at 20°-25°C (68°-77°F) using appropriate radiation shielding. Do not freeze.

This reagent kit is approved for use by persons licensed by the Illinois Emergency Management Agency pursuant to 32 Ill. Code Adm. Section, Section 330.260(a) and 335.4010 or under equivalent licenses of the U.S. Nuclear Regulatory Commission, or an Agreement State.

Patent No. 4,789,736

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