Kit for the Preparation of Technetium Tc 99m Mebrofenin

For Diagnostic Use

DESCRIPTION
Each reaction vial contains a nontoxic, sterile, nonpyrogenic mixture of 45 mg mebrofenin, 0.54 mg (maximum) stannous fluoride dihydrate, SnF2·2H2O, 1.03 mg citric acid (as stannous fluoride dihydrate, SnF2·2H2O), not more than 5.2 mg methylene blue, and 0.59 mg propylparaben. The pH is adjusted with sodium hydroxide or hydrochloric acid prior to lyophilization. The contents of the vials are lyophilized and sealed under nitrogen at the time of manufacture.

The pH of the reconstituted product is 4.2 to 5.7. The structure of mebrofenin is shown below.

When sterile, pyrogen-free sodium pertechnetate Tc 99m injection is added to the vial, the diagnostic agent Technetium Tc 99m Mebrofenin is formed for administration by intravenous injection.

PHYSICAL CHARACTERISTICS
Technetium Tc 99m decay is by isomeric transition with a physical half-life of 6.02 ± 0.02 hours. The principal reaction that is useful for detection and imaging studies is shown in Table 1.

CLINICAL PHARMACOLOGY
Mebrofenin is an imidazoline acid (HIDA) derivative with no known pharmacologic actions at the sites of the injected doses. Following intravenous administration in normal subjects, Technetium Tc 99m Mebrofenin was rapidly cleared from the circulation. The mean percent injected dose remaining in the blood at 10 minutes was 17%. The injected activity was cleared through the hepatobiliary system with visualization of the liver by 5 minutes and maximum liver uptake occurring at 11 minutes postinjection. Hepatic duct and gallbladder visualization occurred by 10 to 15 minutes and intestinal activity was visualized by 30 to 60 minutes in subjects with normal hepatobiliary function. The mean percent injected dose excreted in the urine during the first 3 hours was 1% (0.4 to 2.0%).

Elevated serum bilirubin levels increase renal excretion of Tc 99m HIDA. The mean percent injected dose administered to patients having mean elevated serum bilirubin levels of 9.8 mg/dL (1.7 to 44.3 mg/dL) was the mean percent injected dose excreted in the urine during the first 3 hours was 3.2% (3.2 to 11.5%). The mean percent injected dose excreted in the urine during 3-24 hours was 14.9% (5.4 to 34.9%). The dose remaining in the blood at 10 minutes may be twice as high or more than the level in normals. Hepatobiliary transit may be delayed and visualization times prolonged. As a consequence, the quality of the images frequently diminishes.

INDICATIONS AND USAGE
Technetium Tc 99m Mebrofenin is indicated as a hepatobiliary imaging agent.

CONTRAINDICATIONS
Hypersensitivity to this compound.

WARNINGS
The potential possibility of allergic reactions should be considered in patients who receive multiple doses.

PRECAUTIONS
General
Content of the reaction vial are intended only for use in the preparation of Technetium Tc 99m Mebrofenin and are not to be administered directly to the patient. Delayed or non-visualization of the gallbladder may occur in the immediate postinjection period or after prolonged fasting or parenteral feeding. Functional biliary obstruction may accompany chronic choledocholith or pancreatitis. In addition, patients with hepatorespiratory disease may show non-visualization or delayed visualization of the gallbladder. Delayed intestinal transit may also be noted in such patients. Juvenile hepatitis may be associated with gallbladder non-visualization and the failure to visualize activity in the intestine. Administration of meperidine or morphone may delay intestinal transit of the imaging agent and may result in non-visualization. Steptococcal patients may show absent or delayed hepatobiliary clearance. Thus, a positive finding does not of itself permit a differential diagnosis of any of the above conditions and should be evaluated in the light of the total clinical picture and results of other diagnostic modalities.

The components of the kit are sterile and nonpyrogenic. Acceptable procedures normally employed in making additions and withdrawals from sterile, nonpyrogenic containers should be used during the addition of the pertechnetate solution and the withdrawal of doses for patient administration.

The Technetium Tc 99m labeling reactions involved in preparing the agent depend on maintaining the stannous ion in the reduced state. Any oxidant present in the sodium pertechnetate Tc 99m supply may adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc 99m containing oxidants should not be employed.

Pacemaker/defibrillator should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides. As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to ensure minimum radiation exposure to occupational workers.

To Tc 99m Mebrofenin should be formulated no more than 10 hours prior to clinical use.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies have performed to evaluate carcinogenic potential or whether Technetium Tc 99m Mebrofenin may affect fertility in males or females.

Pregnancy
Pregnancy Category C
Animal reproduction studies have not been conducted with Technetium Tc 99m Mebrofenin. It is also not known whether Technetium Tc 99m Mebrofenin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc 99m Mebrofenin should be given to a pregnant woman only if the expected benefits to be gained clearly outweigh the potential hazards.

Nursing Mothers
Technetium Tc 99m is excreted in human milk during lactation. Therefore, formula feedings should be substituted for breast feedings.

Pediatric Use
Safety and effectiveness in children below the age of 18 have not be established.

ADVERSE REACTIONS
Urticaria and rash have been rarely reported with the use of Technetium Tc 99m Mebrofenin. Rare cases of chills and rigors have been reported with related compounds. Intravascular death has been reported in association with the use of this class of agents.

DOSEAGE AND ADMINISTRATION
The suggested intravenous dose range of Technetium Tc 99m Mebrofenin in the average patient (70 kg) is

Nonpuriposed patient

Serum with serum bilirubin level greater than 1.5 mg/dL

74-185 MBq (2-5 mCi)

111-370 MBq (3-10 mCi)
HOW SUPPLIED
Cholecite (kit for the Preparation of Technetium Tc 99m Methylene) is supplied in kits of 10 reaction vials. Each vial contains a sterile, non-lyophilized lyophilized mixture of 45 mg technetium-99m pertechnetate (0.54 mg (minimum) stannous fluoride dinitrate, SnF₂·2H₂O and 1.03 mg total tin; maximum (as stannous fluoride dinitrate, SnF₂·H₂O), not more than 0.5 mg mephitopon, and 0.98 mg propylparaben. The pH has been adjusted with hydrochloric acid or sodium hydroxide prior to lyophilization. The lyophilized vial contents are sealed under nitrogen at the time of manufacture. The pH of the reconstituted product is 4.2 to 5.7.

Kit Contents
10 sterile multidose reaction vials.
20 pressure-sensitive labels for Technetium Tc 99m Methylene.
1 package insert.

Preparation
Preparation of Technetium Tc 99m Methylene is done by the following aseptic procedure:
1. Waterproof gloves should be worn during the preparation procedure.
2. Place reaction vial in an appropriate lead shield.
3. Saturate the rubber closure of the reaction vial with a germicide.
4. Inject 1 to 5 mL sterile additive free sodium pertechnetate Tc 99m injection containing up to 2700 MBq (100 mCi) Tc 99m into the reaction vial. Be sure to maintain a nitrogen atmosphere in the vial by not introducing air during reconstitution.
5. Secure the lead shield cover. Swirl the vial gently to mix contents and let stand for 15 minutes.
6. Record the date and time of preparation on pressure-sensitive label.
7. Affix pressure-sensitive label to shield.
8. Examine vial contents. If the solution is not clear and free of particulate matter and discoloration on visual inspection, it should not be used.
9. Measure the radioactivity by a suitable calibration system and record on the shield label prior to patient administration.
10. Withdraw material with a sterile lead shielded syringe for use within 18 hours of preparation.

Storage
Store the kit as supplied at 20-25°C (68-77°F) [See USP] prior to and following reconstitution. Use within 18 hours of reconstitution.

The U.S. Nuclear Regulatory Commission has approved this reagent kit for distribution to persons licensed to use byproduct material identified in $353 200 of 10 CFR Part 35, to persons who hold an equivalent license issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

Rx only
Manufactured for Bracco Diagnostics Inc.
Monroe Township, NJ 08831
by Jubilant HolisterStier LLC
Spokane, WA 99207 USA

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TABLE 4
Estimated Absorbed Radiation Dose

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Normal Subjects*</th>
<th>Severe</th>
<th>Jaundiced Patients**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>370 MBq 10 mCi</td>
<td>10 mCi</td>
<td>370 MBq 10 mCi</td>
</tr>
<tr>
<td>Total Body</td>
<td>2.0</td>
<td>0.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Liver</td>
<td>4.7</td>
<td>0.47</td>
<td>8.1</td>
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<tr>
<td>Gallbladder Wall</td>
<td>13.7</td>
<td>1.37</td>
<td>12.5</td>
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<tr>
<td>Spleen</td>
<td>29.9</td>
<td>2.89</td>
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<tr>
<td>Intestine Wall</td>
<td>47.4</td>
<td>4.74</td>
<td>24.8</td>
</tr>
<tr>
<td>Lower Large</td>
<td>30.4</td>
<td>3.64</td>
<td>19.7</td>
</tr>
<tr>
<td>Intestine Wall</td>
<td>3.4</td>
<td>0.22</td>
<td>1.5</td>
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<tr>
<td>Urinary Bladder</td>
<td>2.9</td>
<td>0.29</td>
<td>2.4</td>
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<tr>
<td>Vascular</td>
<td>10.1</td>
<td>1.01</td>
<td>6.4</td>
</tr>
<tr>
<td>Testes</td>
<td>0.5</td>
<td>0.05</td>
<td>1.1</td>
</tr>
<tr>
<td>Red Mucosa</td>
<td>3.4</td>
<td>0.34</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Method of Calculation:

(2) Values for S: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, NIRD Pamphlet No. 11 (1975).

- Bilirubin <1.5 mg/dl:

  Calculations assume that 98% of the injected activity is taken up by the liver; activity not removed in the urine in 24 hours is excreted in the intestines and no enterohepatic circulation of activity.

- Bilirubin >10 mg/dl, (mean 21.5 mg/dl):

  Calculations assume that 66% of the injected activity is taken up by the liver; activity not removed in the urine in 24 hours is excreted in the intestines and no enterohepatic circulation of activity.