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

**Table 3. Physical Decay Chart; Technetium Tc-99m Half-Life 6.02 Hours**

<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>1</td>
<td>0.891</td>
</tr>
<tr>
<td>1</td>
<td>0.794</td>
<td>2</td>
<td>0.708</td>
</tr>
<tr>
<td>3</td>
<td>0.562</td>
<td>6</td>
<td>0.501</td>
</tr>
<tr>
<td>4</td>
<td>0.447</td>
<td>5</td>
<td>0.355</td>
</tr>
<tr>
<td>6</td>
<td>0.316</td>
<td>7</td>
<td>0.282</td>
</tr>
</tbody>
</table>

*Calibration Time

**Clinical Pharmacology:**

**General:** NEUROLITE®, Kit for the Preparation of Technetium Tc-99m Bicisate for Injection forms a stable, lipophilic complex which can cross the blood brain barrier. Technetium Tc-99m Bicisate crosses intact cell membranes and the intact blood brain barrier by passive diffusion. Five percent of the injected dose remains in the blood at one hour. The amount of Technetium Tc-99m Bicisate in the brain is stable until about 6 hours. After background clearance, the brain can be obtained from 10 minutes to 6 hours after injection. Optimal images occur 30-60 minutes after injection. Technetium Tc-99m Bicisate is cleared primarily by the kidneys.

**Pharmacokinetics:** In a study in 16 normals (13 men and 3 women, mean age of 31 ± 10 years; mean weight of 72 ± 11 kg), the pharmacokinetic profile in blood best fits a three compartment model with half-lives of 43 seconds, 49.5 minutes and 533 minutes. The highest concentration of radioactivity measured in blood was found at 0.5 minutes after intravenous injection and was 13.3% of the injected dose. Technetium Tc-99m Bicisate and its major metabolites are not protein-bound.

**Metabolism:** Technetium Tc-99m Bicisate is metabolized by endogenous enzymes to mono- and di-acids of Technetium Tc-99m Bicisate that can be detected in blood and urine. No studies have been performed to compare the concentration of Technetium Tc-99m Bicisate or its metabolites in normal, ischemic and infarcted cells.

**Pharmacodynamics:** Localization of the parent compound in the brain in part depends upon both perfusion of the region and uptake of Technetium Tc-99m Bicisate. The degree of cell function or viability needed for metabolism or its metabolites are dialyzable. Fecal excretion accounts for 12.5% of the injected dose after 48 hours. Technetium Tc-99m Bicisate and its metabolites are not protein-bound.

**Use with caution:**

- **In patients with renal or hepatic impairment:** Technetium Tc-99m Bicisate is eliminated primarily by renal excretion. Whether Technetium Tc-99m Bicisate is dialyzable is not known. Dose adjustments in patients with renal or hepatic impairment have not been studied.
- **In patients with altered kidney function:** Patients should be encouraged to drink fluids and to void frequently between 2-6 hours immediately after injection to minimize radiation dose to the bladder and other target organs.
- **In patients with altered liver function:** Contents of the vials are intended only for use in the preparation of Technetium Tc-99m Bicisate and are not to be administered directly to the patient without first undergoing the preparation procedure.
- **In patients with altered musculoskeletal structure:** The contents of each vial are sterile and non-pyrogenic. To maintain sterility, aseptic technique must be used during all operations in the manipulation and administration of NEUROLITE®.
- **In patients with altered musculoskeletal structure:** Technetium Tc-99m Bicisate should be used within six hours of the time of preparation.
- **In patients with altered musculoskeletal structure:** As with any other radioactive material, appropriate shielding should be used to avoid unnecessary radiation exposure to the patient, occupational workers, and other people.

**Radiopharmaceuticals:** Should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Studies have not been conducted to evaluate carcinogenic potential or effects on fertility. When tested in vitro, NEUROLITE® prepared with decayed generator eluate induced unscheduled DNA synthesis in rat hepatocytes and caused an increased frequency of sister chromatid exchanges in CHO cells; but, it did not induce chromosome aberrations in human lymphocytes or cause gene mutations in the Ames test or in a CHO/HGPRT test. Unreacted bicisate dihydrochloride increased the apparent rate of gene mutation of the TA 97a strain of *S. typhimurium* in the Ames test; but, it did not demonstrate clastogenic activity in an in vivo micronucleus assay in mice.

**Pregnancy:**

- **Teratogenic Effects:**
  - **Pregnancy Category C:** Animal reproduction studies have not been conducted with Technetium Tc-99m Bicisate. It is also not known whether Technetium Tc-99m Bicisate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, Technetium Tc-99m Bicisate should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.
Radiochemical purity should be checked before administration to the patient. The dose for the patient should be measured by a suitable radioactivity calibration method. Gender or renal or hepatic impairment have not been studied. The patient is 370 - 1110 MBq (10-30 mCi). Dose adjustments for age, weight, 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. NEUROLITE® is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to assess renal function prior to administration.

ADVERSE REACTIONS
In clinical trials, NEUROLITE® has been administered to 1063 subjects (255 normals, 808 patients). Of these, 566 (53%) were men and 494 (47%) were women. The mean age was 58 years (range 17 to 92 years). In the 808 patients who had experienced neurologic events, there were 11 (1.4%) deaths, none of which were clearly attributed to NEUROLITE®. A total of 60 subjects experienced adverse reactions; the adverse reaction rates were comparable in the <65 year, and the ≥65 year age groups. The following adverse effects were observed in ≤1% of the subjects: headache, dizziness, seizure, agitation/anxiety, malaise/somnolence, parosmia, hallucinations, rash, nausea, syncope, cardiac failure, hypertension, angina, and apnea/cyanosis. In clinical trials of 197 patients, there were inconsistent changes in the serum calcium and phosphate levels. The cause of the changes has not been identified and their frequency and magnitude have not been clearly characterized. None of the changes required medical intervention.

DOSAGE AND ADMINISTRATION:
Prior to reconstitution, vial A and vial B are stored at 15-25°C. Protect vial A from light. With a sterile syringe, aseptically add 3.70 GBq (100 mCi) sterile, sodium chloride injection (0.9%) into vial A (the lyophilized vial) to dissolve the contents. Remove the plastic disc from both vials and swab the top of each vial with a pencil, draw a faint line across the TLC plate at heights of two (2) cm, four and one half (4.5) cm and seven (7) cm from the bottom of the TLC plate. Place approximately 5 µl of the final solution at the center of the 2 cm mark. This can be accomplished using a syringe fitted with a 25 or 27 gauge needle and allowing a drop to form while holding the syringe in a vertical position. The diameter of the spot should not be greater than 10 mm. Allow the spot to dry for 5 to 10 minutes, no longer.

TLC PROCEDURE
Establish the radiochemical purity (RCP) of the final solution by the thin layer chromatography (TLC) using Baker-Flex silica gel IB-F plates and a solvent system of ethyl acetate. The RCP should be ≥90%.

Procedure - Using fresh ethyl acetate pour enough solvent into the developing tank to a depth of 3 to 4 mm. Seal the tank with Parafilm and allow 15 to 30 minutes for solvent equilibration. It is important to pre-equilibrate and preserve the integrity of the headspace in the chromatographic tank, otherwise unreproducible TLC results are obtained. Note: Ethyl acetate is a skin/mucous membrane irritant and should be handled in a hood whenever possible.

Place the TLC plate at the 4.5 cm mark with scarcers. Count the activity on each piece using a dose calibrator or a gamma counter. The top portion contains the Technetium 99m Bicisate and the bottom portion contains all radioimpurities.

Calculate the radiochemical purity using the following equation:

\[ \text{% Technetium 99m Bicisate} = \frac{A_t}{A_t + A_b} \times 100 \]

Where: \( A_t \) = activity of the top piece and \( A_b \) = activity of the bottom piece.

HOW SUPPLIED: Lantheus Medical Imaging, Inc. NEUROLITE® Kit for the Preparation of Technetium 99m Bicisate for Injection, is supplied in kits of two (2) vials of A and two (2) vials of B (NDC # 11994-006-02), and five (5) vials of A and five (5) vials of B (NDC # 11994-006-05). Included in each kit are one (1) package insert and twelve (12) radiation labels.

Prior to reconstitution, vial A and vial B are stored at 15-25°C. Protect vial A from light. Store at controlled room temperature after preparation. Use within 6 hours of preparation.