The Du Pont Merck Pharmaceutical Company
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NEUROLITE®
Kit for the Preparation of Technetium Tc99m Bicisate Injection

For Diagnostic Use

DESCRIPTION: This kit formulation consists of two nonradioactive vials**:**
Vial A contains bicisate dihydrochlonde (N, N'-1,2-ethylenediy(bis-L-cysteine diethyl ester dihydrochloride) and a reducing agent as a lyophilized solid and vial B contains a buffer solution. Both vials are sterile and non-pyrogenic.

Vial A -

Bicisate dihydrochloride (ECD•2HCl)	0.9mg
Edetate disodium. dihydrate	0.36mg
Mannitol	24mg
Stannous chloride, dihydrate, theoretical ($SnCl_2$•$2H_20$)	72ug
Stannous chloride, dihydrate minimum ($SnCl_2$•$2H_20$)	12ug
Total Tin. (stannous and stannic), dihydrate (as $SnCl_2$•$2H_2O$)	83ug

The contents of vial A are lyophilized and stored under nitrogen. The pH of the solution before lyophilization is 2.7 ±0.25. This vial is stored at 15-25°C. Protect from light.

Vial B-

Sodium phosphate dibasic heptahydrate	4.1 mg
Sodium phosphate monobasic monohydrate	0.46mg
Water for Injection	qs 1ml

The contents of vial B are stored under air. The pH of the solution is 7.6 ± 0.4. This vial is stored at 15-2S°C.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic. oxidant-free Sodium Pertechnetate Tc99m Injection. The precise structure of the Technetium complex is [N,N'-ethylenedi-L-cysteinato(3-)]oxo[^{99m}Tc] technetium (V), diethyl ester**.**

PHYSICAL CHARACTERISTICS
Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours[1]. The principal photon that is useful for detection and imaging studies is listed in Table 1.

TABLE 1.

Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

[1]Kocher, David C., 'Radioactive Decay Data Tables", DOE/TIC-11026, 108, 1981

External Radiation

The specific gamma ray constant for Tc99m is 5.4 microcoulombs/kg-MBq-hr (0.78R/mCi-hr) at 1cm. The first half value layer is 0.017cm of lead (Pb). Relative attenuation of the radiation emitted ay this radionuclide results from interposition of various thicknesses of Pb. The corresponding attenuation is shown in Table 2. To facilitate control of the radiation exposure from MBq (mCi) amounts of this radionuclide a 0.25cm thickness of Pb will attenuate the radiation by a factor of 1,000.

Table 2.

Radiation Attenuation by Lead Shielding

Shield Thickness (Pb)cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

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

TABLE 3.

Physical decay Chart: Tc 99m Half-Life, 6.02 hours			
Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	5	0.562
1	0.891	6	0.501
2	0.794	8	0.398
3	0.708	10	0.316
4	0.631	12	0.251

'*Calibration time.

CLINICAL PHARMACOLOGY:

General: Neurolite®, Kit for the Preparation of Technetium Tc99m Bicisate injection forms a stable, lipophilic complex which can cross the blood brain barrier. Technetium Tc99m 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 Tc99m Bicisate in the brain is stable until about 6 hours. After background clearance, images of the brain can be obtained from 10 minutes to 6 hours after injection. Optimal images occur 30-60 minutes after injection. Technetium Tc99m 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 13.9% of the injected dose. Technetium Tc99m Bicisate and its major metabolites are not protein-bound.

Metabolism: Technetium Tc99m Bicisate is metabolized by endogenous enzymes to the mono- and di-acids of Technetium Tc99m Bicisate that can be detected in blood and urine. No studies have been performed to compare the concentration of Technetium Tc99m Bicisate or its metabolites in normal, ischemic and infarcted cells.

Technetium Tc99m Bicisate is excreted primarily through the kidneys. Within two hours, 50% of the injected dose is excreted and by 24 hours, 74% is found in urine. It is not known whether the parent drug molecule or its metabolites are dialyzable. Fecal excretion accounts for 12.5% of the injected dose after 48 hours.

Pharmacodynamics: Localization of the parent compound in the brain in part depends upon both perfusion of the region and uptake of Technetium Tc99m Bicisate by the cell. Once in the brain cells, the parent compound is metabolized to polar, less diffusible compounds. Studies in 21 normal volunteers show cellular uptake of 4.8-6.5% of the injected dose at five minutes after injection. The degree of cell function or viability needed for uptake is not known. The degree of cell function or viability needed for metabolism of the parent compound to the less diffusible compounds has not been determined. The likelihood that the metabolic pathway is damaged by ischemia is not known. Whether or not and to what extent uptake correlates with viability or function is not known.

The pharmcodynamics of Neurolite have not been evaluated for differences associated with age, gender, weight and liver or renal impairment. It is not known whether dosage adjustments for these factors are needed.

Clinical Trials: Two clinical trials were performed in a total of 359 subjects, (273 with stroke, 86 normal). Of these 56% were men and 44% were women. The mean age was 60.2 years (range 23 to 92 years). Subjects were 87.2% Caucasian, 8.4% Black, 2.2% Hispanic, 1.7% Oriental and 0.6% other.

Eligible Patients had a confirmed stroke. Patients with other brain lesions were not evaluated. Subjects received Neurolite (mean dose range 10-30mCi) and underwent SPECT imaging and either CT or MRI scans within 0-30 days of the onset of signs and symptoms of stroke. CT or MRI and the administration of Neurolite occurred at different and variable times after the onset of a stroke. The effect of the timing on the accuracy of the images cannot be evaluated. The Neurolite scan results were blindly compared to unblended CT/MRI results, the short standardized neurologic examination (SSNE) and the final diagnosis (e.g. the overall combined clinical impression with CT/MRI and SSNE).

In these studies, at least one of three blinded readers mace a diagnosis of stroke in 190 (85%) of the Neurolite SPECT studies and in 238 (88%) CT/MRI studies. The Neurolite and CT/MRI imaging results versus the SSNE and final diagnosis were comparable. Neurolite had 11 false positives and 34 false negatives. CT/MRI had 0 false positive and 31 false negatives. Both Neurolite and CT/MRI missed strokes (true positives) that were identified by the other modality. The majority of the false negatives in either modality were within 15 days of the clinical stroke.

The trials were not designed to determine when Neurolite or CT/MRI studies could become positive in relationship to the time of the stroke. The relevance of the Neurolite scan results to the prediction of neurologic function or brain cell viability is not known. Also not known is the ability of the Neurolite findings to distinguish between a stroke and pre-existing CNS lesions. Neurolite should not be used for these purposes. (See Pharmacodynamics Section).

INDICATIONS: Neurolite single photon emission computerized tomography (SPECT) is indicated as an adjunct to conventional CT or MRI imaging in the localization of stroke in patients in whom stroke has already been diagnosed.

Neurolite is not indicated for assessment of functional viability of brain tissue. Also, Neurolite is not indicated for distinguishing between stroke and other brain lesions.

CONTRADICTIONS
None known.

WARNINGS
None known.

PRECAUTIONS
General
USE WITH CAUTION IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT. TECHNETIUM Tc99m BICISATE IS ELIMINATED PRIMARILY BY RENAL EXCRETION. WHETHER TECHNETIUM Tc99m BICISATE IS DIALYZABLE IS NOT KNOWN. DOSE ADJUSTMENTS IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT HAVE NOT BEEN STUDIED.

Patients should be encouraged to drink fluids and to void frequently during the 2-6 hours immediately after injection to minimize radiation dose to the bladder and other target organs.

Contents of the vials are intended only for use in the preparation of Technetium Tc99m Bicisate and are not to be administered directly to the patient without first undergoing the preparation procedure.

The contents of each vial are sterile and non-pyrogenic. To maintain sterility, aseptic technique must be used during all operations in manipulation and administration of Neurolite.

Technetium Tc99m Bicisate should be used within six hours of the time of preparation.

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. typhimunum* in the Ames test but it did not demonstrate clastogenic activity in a vivo micronucleus assay in mice.

Pregnancy: Teratogenic Effects
Pregnancy Category C
Animal reproduction studies have not been conducted with Technetium Tc99m Bicisate. It is also not known whether Technetium Tc99m Bicisate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, Technetium Tc99m Bicisate should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Technetium Tc99m Pertechnetate can be excreted in human milk. Therefore, formula should be substituted for breast milk until the technetium has cleared from the body of the nursing woman.

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

ADVERSE REACTIONS
In clinical trials, Neurolite has been administered to 1022 subjects (262 normals, 760 patients). Of these, 548 (54%) were men and 473 (46%) were women. The mean age was 58 years (range 17 to 92 years).

In the 750 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: Before administration, a patient should be well hydrated. After administration, the patient should be encouraged to drink fluids liberally and to void frequently.
The recommended dose range for intravenous administration for a 70kg patient is 370 - 1110 MBq (10-30 mCi). Dose adjustments for age, weight, gender or renal or hepatic impairment nave not been studied.

The dose for the patent should be measured by a suitable radioactivity calibration system immediately before administration to the patient. Radiochemical purity should be checked before administration to the patient.
Neurolite, like other parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Preparations containing particulate matter or discoloration should not be administered. They should be disposed of in a safe manner in compliance with all applicable regulations.

Prior to reconstitution, vial A and vial B are stored at 15-25 degrees C. Protect vial A from light.

Store at room temperature (15-30 degrees C) after preparation.

Aseptic techniques and effective shielding should be employed in withdrawing doses for administration to patients. Waterproof gloves and effective shielding should be worn when handling the product.

RADIATION DOSIMETRY: The radiation doses to organs and tissues of an average patient (70kg) for Technetium Tc99m Bicisate injected intravenously for 370 MBq (10 mCi) are shown in Table 4 and for 1110 MBq (30 mCi) are shown in Table 5.

Table 4. **Radiation Absorbed Dose From 370 MBq (10 mCi) of Technetium Tc99m Bicisate**

	Estimated Absorbed Radiation Dose[2]			
	2.0 Hour Void		4.8 Hour Void	
	mGy/370 MBq	rads/10 mCi	mGy/370 MBq	rads/10 mCi
Organ				
Bone Surface	1.26	0.13	1.41	0.14
Brain	2.04	0.20	2.04	0.20
Gallbladder Wall	9.25	0.91	9.25	0.92
Intestine Wall (Lower Large)	4.81	0.47	5.55	0.55
Intestine Wall (Small)	3.48	0.35	3.70	0.38
Intestine Wall (Upper Large)	5.92	0.61	6.29	0.63
Kidneys	2.70	0.27	2.74	0.27
Liver	1.96	0.20	2.00	0.20
Lungs	0.74	0.08	0.74	0.08
Ovaries	2.00	0.20	2.96	0.30
Red Marrow	0.89	0.09	1.0	0.10
Testes	0.81	0.08	1.33	0.13
Thyroid	1.30	0.13	1.30	0.13
Urinary Bladder Wall	11.10	1.10	27.01	2.70
Total Body	0.89	0.09	1.07	0.11

Table 5. **Radiation Absorbed Dose From 1110 MBq (30 mCi) of Technetium Tc99m Bicisate**

	Estimated Absorbed Radiation Dose[2]			
	2.0 Hour Void		4.8 Hour Void	
	mGy/370 MBq	rads/10 mCi	mGy/370 MBq	rads/10 mCi
Organ				
Bone Surface	3.77	0.39	4.22	0.42
Brain	6.11	0.61	6.11	0.61
Gallbladder Wall	27.75	2.73	27.75	2.76
Intestine Wall (Lower Large)	14.43	1.41	16.65	1.65
Intestine Wall (Small)	10.43	1.05	11.10	1.14
Intestine Wall (Upper Large)	17.76	1.83	18.87	1.89
Kidneys	8.10	0.81	8.21	0.81
Liver	5.88	0.60	5.99	0.60
Lungs	2.22	0.23	2.22	0.23
Ovaries	5.99	0.66	8.88	0.90
Red Marrow	2.66	0.26	3.00	0.29
Testes	2.44	0.24	4.0	0.39
Thyroid	3.89	0.39	3.89	0.39
Urinary Bladder Wall	33.33	3.33	81.03	8.10
Total Body	2.66	0.27	3.22	0.33

[2]Dosimetry calculated using the MIRD software program at Oak Ridge Associated Universities, P. O. Box 117, Oakridge, TN, 29 July 1988.

INSTRUCTIONS FOR PREPARTION OF TECHNETIUM Tc99m BICISATE

Preparation of the TechnetiumTc99m Bicisate from the NEUROLITE® Kit for the Prepartion of Techntium Tc99m Bicisate Injection is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertehcnetate Tc99m injection to vial B (the liquid vial), write the estimated activity, date and time of preparation in the space provided on the vial label. Then 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 both vials and swab the top of each vial closure with alcohol to disinfect the surface.
c. Place vial B in a suitable radiation shield appropriately labeled with date, time of preparation, volume and activity.
d. With a sterile shielded syringe, aseptically add 3.70 GBq (100 mCi) sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection, in approximately 2.0 ml, to vial B. Without withdrawing the needle, remove an equal volume of air to maintain pressure within the vial.
e. With a sterile syringe, rapidly inject 3.0 ml of Sodium Chloride Injection (0.9%) into vial A (the lyophilized vial) to dissolve the contents. Without withdrawing the needle, remove an equal volume of air to maintain pressure within the vial. Shake the contents of the vial for a few seconds.
f. With another sterile syringe, immediately (within 30 seconds) withdraw 1.0 ml of vial A and inject it into vial B. Discard vial A immediately.
g. Swirl the contents of the vial B for a few seconds and allow this mixture to stand for thirty (30) minutes at room temperature.
h. Examine the vial contents for particulates and discoloration prior to patient administration. If particulate matter and/or discoloration are seen DO NOT USE.
i. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium Tc99m concentration, total volume, assay time and date, espiration time and lot number on the vial shield label and affix the label to the shield.
j. Store the reaction vial containing the Technetium Tc99m Bicisate at room temperature (15-30°C) until use: at such time the product should be aseptically withdrawn. The vial contains no preservative.

Note: Adherence to the above reconstitution instructions is recommended.
Product should be used within 6 hours of preparation.

DETERMINATION OF RADIOCHEMICAL PURITY

The preparation and quality control of the agent should follow the procedure shown below.

MATERIALS FOR TLC PROCEDURE

Bakerflex silica gel 1B-F, 2.5 x 7.5 cm, Baker #4463-03
Solvent system: Ethyl Acetate, HPLC grade
Dose calibrator or gamma counter for measuring radioactivity
Small chromatographic developing tank
Syringe and shielded vials, as needed

TLC PROCEDURE

Establish the radiochemical purity (RCP) of the final solution by the thin layer chromatography (TLC) using Baker-Flex silica gel 1B-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 irreproducible TLC results are obtained. Note: ethyl acetate is a skin/mucous membrane irritant and should be handled in a hood wherever possible.

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 5µL 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 thn 10 mm. Allow the spot to dry for 5 to 10 minutes, no longer.

Place the plate in the pre-equilibrated TLC tank and develop to the 7.0 cm line (about 15 minutes). Remove the plate and dry in a ventilated area.

Quantification

Cut the TLC palate at the 4.5 cm mark with scissors. Count the activity on each piece using a dose calibrator or a gamma counter. The top portion contains the Technetium Tc99m Bicisate and the bottom portion contains all radioimpurities.

Calculate the radiochemical purity using the following equation:

$$\% \text{ Technetium Tc99m Bicisate} = \frac{A_T}{A_T + A_B} \text{ X } 100$$

Where A_T = activity of the top piece and A_B = activity of the bottom piece.

HOW SUPPLIED: DuPont Radiopharmaceutical's Neurolite® for the Prepartion of Techneitum Tc99m Bicisate Injection is supplied in kits of two (2) vials of A and two (2) vials of B and five (5) vials of A and five (5) vials of B. 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 room temperature (15-30°C) after preparation.

use within 6 hours of preparation.

The U.S. Nuclear Regulatory Commission has approved this reagent kit for distribution to persons licensed to use byproduct material pursuant to section 35.11 and section 35.200 of 10 CFR Part 35, to persons who hold an equivalent license issued by an Agreement State, and outside the United Satates, to persons authorized by the appropriate authority.

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